Synthesis of Some Thiophene, Imidazole and Pyridine Derivatives Exhibiting Good Anti-Inflammatory and Analgesic Activities

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Abstract: A series of thiophene derivatives **1a-d** & **2a-c** were synthesized by condensation of 5-nitro-2-thiophene carboxaldehyde with mono and diamines respectively. Various imidazole derivatives **3a-c** were obtained by condensing 4-(2-ethylamino)-1H-imidazole with 4-acetylpyridine, 2-acetylpyridine and 4-acetylbenzonitrile respectively. Pyridine derivatives **4a-e** were synthesized by condensing 2-hydrazino-pyridine with various carbonyl compounds; **5a-c** by condensing 2, 6-pyridine dicarbonyl dichloride with various aryl sulfonylhydrazides; **6, 7** by condensing 2, 6-dialdehyde pyridine with 2-hydrazinopyridine and anthranilonitrile respectively and compound **8** by condensing 2, 5-thiophene dialdehyde with hydrazinopyridine. All the compounds were characterized by IR, ^{1}HNMR, Mass spectra and elemental analysis. Compounds **1a-d**; **2a-c**; **3a-c**; **4a-e**; **5a-c, 6, 7** and **8** were screened for anti-inflammatory and analgesic activities. Compounds **1b** and **2c** exhibited good anti-inflammatory (26.5% and 33.4% at 50mg/kg p.o. respectively) and **3a, 3c** good analgesic (100% and 75% at 100 mg/kg p.o. respectively) activities.

Key Words: Thiophene, imidazole, pyridine, anti-inflammatory, analgesic.

1. INTRODUCTION

Thiophene [1-3], imidazole [4-7] and pyridine [8-10] derivatives possessing anti-inflammatory and analgesic activities form an important part of heterocyclic compounds. Apart from the above mentioned activities, thiophene and imidazole derivatives exhibiting antidepressant [11-13], antitumor [14, 15], anti-tuberculosis [16, 17] activities and pyridine derivatives exhibiting antimicrobial [18], antibacterial [19], anti HIV [20] activities have also been reported in the literature.

Tempted by wide varieties of biological activities exhibited by thiophene, imidazole and pyridine derivatives and in the continuation of our efforts [21-24] in search of bioactive molecules, we have synthesized a number of thiophene, imidazole and pyridine derivatives and screened them for anti-inflammatory and analgesic activities, which we wish to report in this paper.

2. RESULTS AND DISCUSSION

2.1. Chemistry

5-Nitro-2-thiophene carboxaldehyde on condensation with 2-hydrazino pyridine by refluxing in THF for 2 hrs gave condensation product **1a** in 50% yield (Scheme **1**). Spectral data of **1a** reported in the experimental section of this paper fully support the structure assigned to it. Condensation of 4-(2-ethyl amino)-1H-imidazole with 5-nitro-2-thiophene carboxaldehyde was done by refluxing in absolute methanol for ten hours and then the crude product was purified by column chromatography over silica gel to give pure product **1b** (Scheme **1**) in 20% yield. Spectral data of **1b** reported in the experimental section of this paper are in complete agreement with the structure assigned to it.

1-(3-Aminopropyl)-imidazole on refluxing with 5-nitro-2-thiophene carboxaldehyde using methanol as solvent of reaction gave condensation product **1c** (Scheme **1**) on usual workup and recrystallization from methanol. Spectral data of **1c** fully support the structure assigned to it. Similarly, condensation of 2-aminobenzothiazole with 5-nitro-2-thiophene carboxaldehyde gave condensed product **1d** in 55% yield. Spectral data of **1d** reported in the experimental section of this paper fully support the structure assigned to it. 1, 4-Bis-(3-aminopropyl) piperazine on refluxing with 5-nitro-2-thiophene carboxaldehyde (2 molar) using methanol as solvent of reaction gave condensed product **2a** in 30% yield. Spectral data and elemental analysis of **2a** fully support the structure assigned to it. Similarly, condensation of 2,4,8, 10-tetraoxaspiro 5,5 undecane-3,9-dipropanamine; and 3,5-diamino-1,2,4-triazole with 5-nitro-2-thiophene carboxaldehyde gave condensed products **2b** and **2c** respectively. Spectral data of **2b** and **2c** reported in experimental section of this paper fully support the structures assigned to them.

4-(2-Ethylamino)-1H-imidazole and 4-acetyl pyridine were heated under reflux for 10 hrs using absolute methanol as the solvent of the reaction. Removal of the solvent and purification of the crude product by column chromatography over silica gel (Elution with ethyl acetate : MeOH 7 : 3) gave pure condensation product **3a** (Scheme **2**) in 55% yield.

Spectral data of **3a** completely support the structure assigned to it. Condensation of 2-acetyl pyridine and 4-acetylbenzonitrile with 4-(2-ethylamino)-1H-imidazole was carried out by heating the reactant (neat) at 120^{o}C for two hours. Crude products **3b** and **3c** obtained respectively were purified by crystallization (MeOH) and by column chromatography over silica gel (elution $CHCl_3$: MeOH : 99 : 1) respec-

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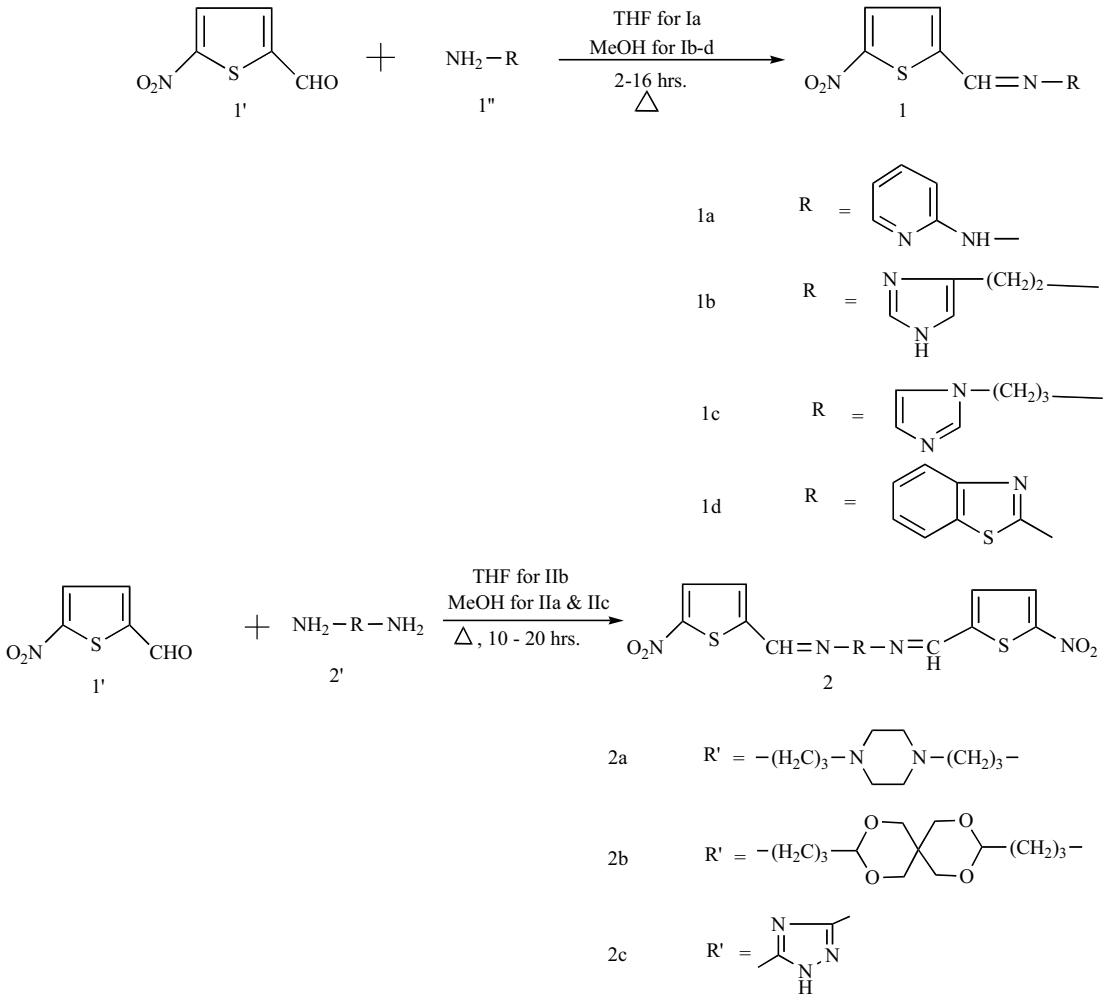
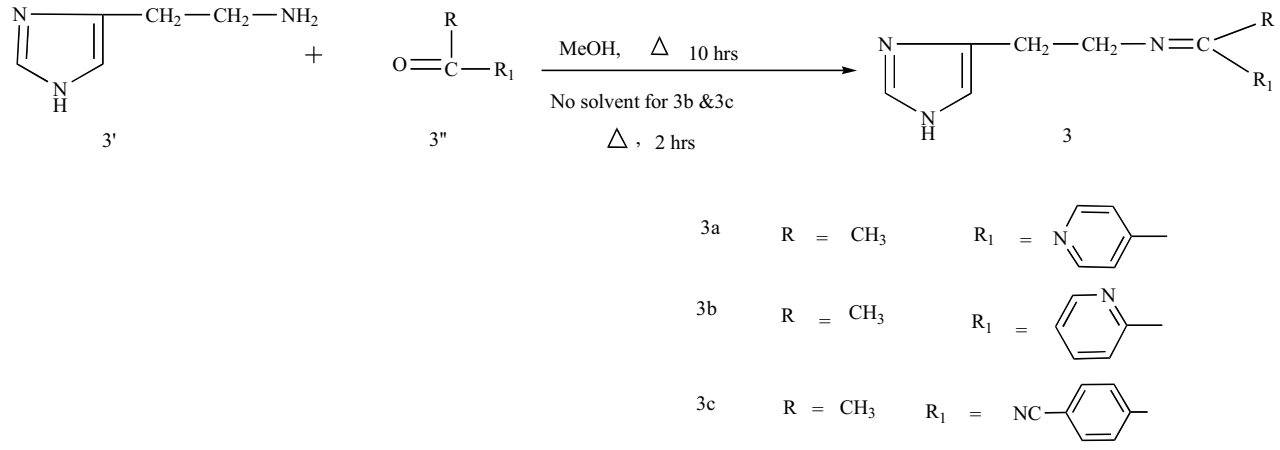


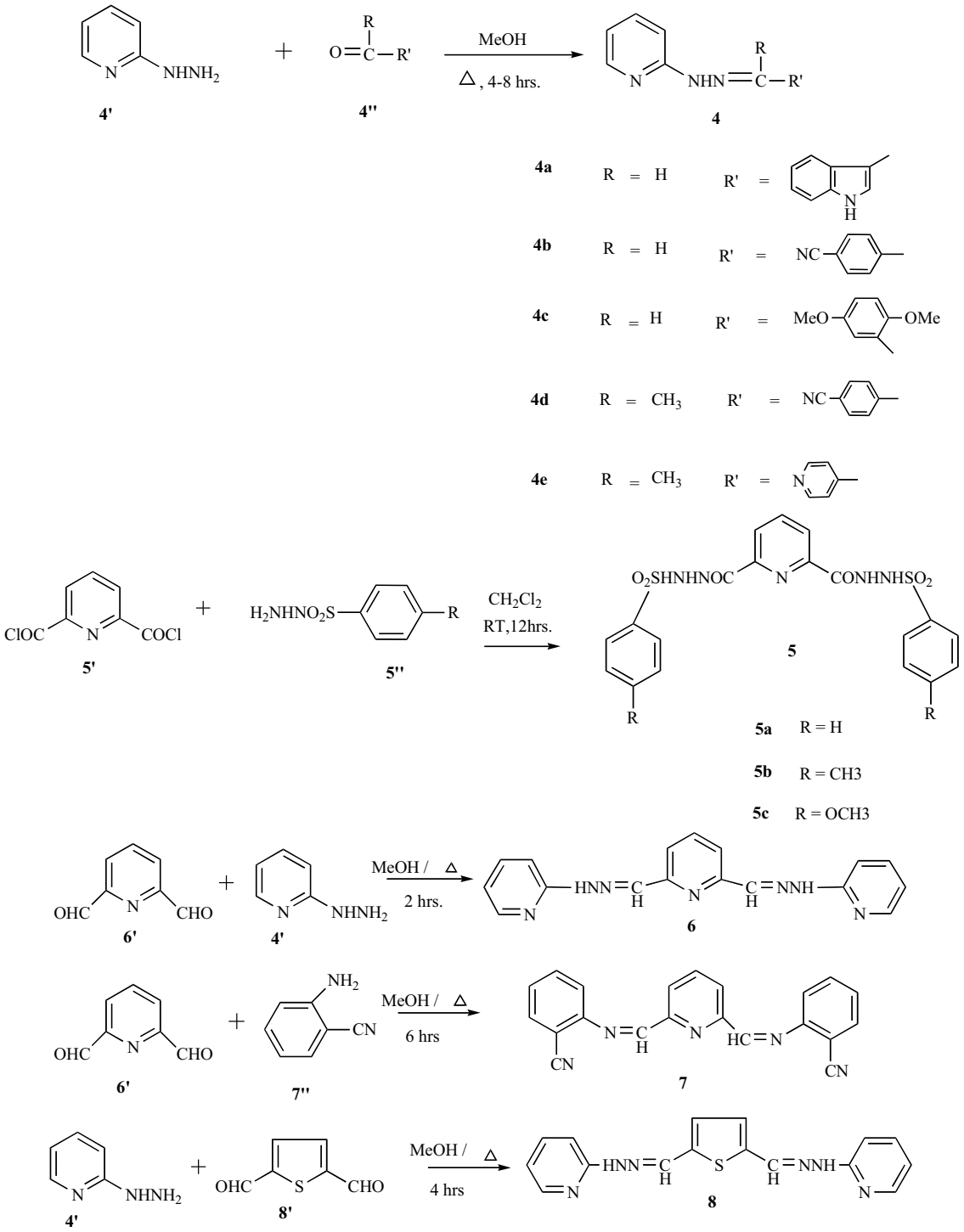
Scheme 1.

tively to give pure products **3b** and **3c**. Spectral data of **3b** and **3c** reported in the experimental section of this paper are in complete agreement with the structures assigned to them.

2-Hydrazinopyridine on condensation with indole-3-carboxaldehyde by refluxing in methanol for 4 hours gave condensed product **4a** (Scheme **3**) in 85% yield. Spectral data of **4a** reported in the experimental section of this paper



Scheme 2.



Scheme 3.

fully support the structure assigned to it. When 4-cyanobenzaldehyde was heated under reflux with 2-hydrazinopyridine using methanol as solvent of reaction, the condensed product **4b** was obtained after five hours. Compound **4b** (Scheme **3**) was purified by recrystalization from methanol. Spectral data of **4b** is in agreement with the structure assigned to it. Similarly, condensation of 2, 5-dimethoxybenzaldehyde, 4-acetylbenzonitrile and 4-acetylpyridine with 2-hydrazinopyridine gave products **4c**, **4d** and **4e** (Scheme **3**) respectively. Physical constants and Spectral data of **4c-e** are reported in the experimental section of this paper and fully confirm the structures assigned to them.Benzene sulfonyl hydrazide and

Table 1. Antiinflammatory and Analgesic Activity Evaluation of 1a-d, 2a-c, 3a-c, 4a-e, 5a-c, 6, 7 and 8

Compound No.	Dose mg/kg p.o.	Antiinflammatory Activity %	Dose mg/kg p.o.	Analgesic Activity %
1a	50	20.0	50	40
1b	50	26.5	50	20
1c	100	24.6	100 50	25 0.0
1d	50	14.6	50	12.0
2a	100	19.0	100 50	75 25
2b	50	22.4	50	10
2c	50	33.4	50	20
3a	100	0.0	100 50	100 75
3b	100	0.0	100 50	75 25
3c	100	0.0	100 50	75 75
4a	50	17.0	50	15
4b	50	18	50	10
4c	50	15	50	10
4d	50	24	50	21
4e	50	16.4	50	17
5a	100	0.0	100	0.0
5b	100	0.0	100	0.0
5c	100	7.0	100	50
6	50	12	50	15
7	50	10	50	20
8	50	22	50	15
Phenyl butazone	100 50 25	58 37 19	100 50 25	58 40 24

2,6-pyridine dicarbonyl dichloride were separately dissolved in dichloromethane and then mixed together and the reaction contents were allowed to stir at room temperature for three hours. Solid product separated out during the reaction, were filtered and washed with a small amount of diethyl ether. This combined products was suspended in 10% sodium carbonate solution and allowed to stir at room temperature for ten minutes and then filtered, washed with water and recrystallized from methanol to give pure product **5a** (Scheme **3**) in 80% yield. Similarly p-toluene sulfonyl hydrazide and 4-methoxybenzene sulfonyl hydrazide were condensed with 2, 6-pyridine dicarbonyl dichloride to give condensation products **5b** and **5c** respectively. Spectral data and physical constants of **5a-c** are reported in the experimental section of this paper and fully confirm the structures assigned to **5a, 5b** and **5c** (Scheme **3**) 2, 6-Dialdehyde pyridine and 2-hydrazinopyridine in the mole ratio of 1:2 were heated under reflux for 2 hours in using methanol, as solvent of reaction. A solid product started separating out during refluxing. After two hours of refluxing the solvent was removed and the crude

product so obtained was purified by crystallization to give condensed product **6** (Scheme **3**) in 85% yield. Spectral data of **6** is in agreement with the structure assigned to it Pyridine derivative **7** (Scheme **3**) was synthesized by refluxing 2,6-dialdehyde pyridine with anthranilonitrile for six hours in methanol as solvent of reaction. Compound **7** was purified by recystallization from methanol. Similarly, condensation of 2- hydrazinopyridine with 2,5-thiophene dialdehyde gave product **8** (Scheme **3**) in 85% yield. Spectral data of **7** and **8** fully support the structures assigned to them and is reported in the experimental section of this paper.

3. BIOLOGICAL RESULTS

Compounds **1a-d**, **2a-c**, **3a-c**, **4a-e**, **5a-c, 6, 7** and **8** were screened for antiinflammatory activity in carrageenin induced paw edema model [25] and for analgesic activity using phenylquinone writhing assays [26] and results are summarized in Table **1**. A look at Table **1** indicates that compounds **1b** and **2c** exhibited good anti-inflammatory activity (26.5% and 33.4% at 50 mg/kg p.o. respectively) and compounds **3a** and **3c** possess good analgesic activity (100% and 75%at 100mg/kg p.o. respectively).

The structures of all the compounds reported in Table **1** and their corresponding anti-inflammatory activity reveals that the compounds possessing thiophene ring system exhibited anti-inflammatory activity but when the compounds were having imidazole or triazole ring system along with thiophene ring present in the molecule i.e. **1b** and **2c** there was increase in the anti-inflammatory activity. Since sulphur of thiophene is a good donor of electron and imidazole or triazole can release proton, this combined property of electron donation and proton release may have contributed in increasing the anti-inflammatory activity of **1b** and **2c** as compared to other compounds reported in Table **1**. From Table **1** it is also clear that imidazole moiety containing compounds have shown good analgesic activity i.e. **3a** and **3c**. It seems that proton releasing property of imidazole may be responsible for exhibiting good analgesic activity.

4. CONCLUSION

A number of thiophene **1a-d**, **2a-c**, imidazole, **3a-c** and pyridine **4a-e**, **5a-c**, **6-8** derivatives have been synthesized and characterized by spectroscopic means & elemental analysis. These compounds were screened for anti-inflammatory and analgesic activities. Thiophene derivatives **1b** & **2c** exhibited good anti-inflammatory and imidazole derivatives **3a** & **3c** good analgesic activities respectively.

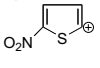
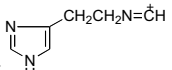
5. EXPERIMENTAL SECTION

Melting points (m.p.) were determined on a JSGW apparatus and are uncorrected. IR spectra were recorded using a Perkin Elmer 1600 FT spectrometer. ^{1}HNMR spectra were measured on a Bruker WH-500, 300 and 200 spectrometer at a Ca. 5-15% (w/v) solution in DMSO-d_6 or $CDCl_3$ (TMS as internal standard). FAB-MS was recorded on JEOL SX-120 (FAB) spectrometer. GC-MS was recorded on Perkin Elmer Clarus 500 mass spectrometer. Elemental analysis was carried out on Vario ELIII elementor.Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized either by iodine vapour or by irradiation with ultraviolet light (254 nm). Column chromatography was performed by using Qualigens silica gel for column chromatography (60-120 mesh).

4.1. Synthesis of N-(5-nitro-thiophen-2yl methylene)-N-pyridin-2-yl Hydrazine (1a)

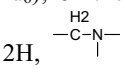
5-Nitro-2-thiophene carboxaldehyde (0.16 g; 1 mmol) was taken in THF (10 ml) and to it was added 2-hydrazinopyridine (0.109 g; 1 mmol). The reaction contents were heated under reflux. After half an hour of refluxing some product started separating out and the reaction was continued to reflux for two additional hours. The solvent was removed under reduced pressure and the crude product so obtained was crystallized from methanol to give pure product **1a**. Yield 0.125 g (50%); mp 260^{O}C. IR(KBr) ν_{max} 3106 (NH), 1610 (C=N), 1568 (Ar) cm^{-1} , ^{1}HNMR (200 MHz; $CDCl_3$) δ 6.80 (t, 1H, Py.), 7.00 (d, 1H, Py), 7.40 (d, 1H, Py), 7.60 (t, 1H, Py.), 7.80 (d+s, 2H, 1H Ar + 1H, -CH=N-), 8.20 (d, 1H, Py.) 8.50 (bs, 1H, NH, exch.), TOF-MS m/z 249.0667 (MH^+, 100%). Anal.. Calcd for $C_{10}H_8N_4O_2S$ C, 48.38; H, 3.22; N, 22.58; S, 12.90. Found C, 48.18; H, 3.15; N 23.02; S, 12.97

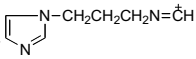
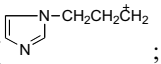
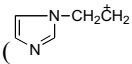
4.2. Synthesis of [2-(1H-Imidazol-4-yl)-ethyl]-(5-nitro-thiophen-2-yl methylene) Amine (1b)

4-(2-Ethylamino)-1H-imidazole (0.222 g; 2 mmol) was taken in methanol (20 ml) and to it was added 5-nitro-2-thiophene carboxaldehyde (0.16 g; 1 mmol). The reaction contents were heated under reflux for ten hours and then the solvent was removed under reduced pressure. The crude product so obtained was purified by column chromatography over silica gel. Elution with $CHCl_3$: ethyl acetate (1 : 1) gave pure product **1b.** Yield 0.100g (20%); mp 250 ^{0}C IR (KBr) ν_{max} 3434 (NH) 1627 (C=N) 1493 (Ar) cm^{-1} . ^{1}HNMR (300 MHz; $CDCl_3$ + DM50-d_6); δ 2.89 (t, 2H, -CH_2-), 4.0 (t, 2H, N-CH_2-), 7.5 (2s, 3H, 2H of imidazole ring + -CH=N-), 7.90 (d, 1H, Ar), 8.40 (d, 1H, Ar), 12.60 (bs, 1H, NH, exch.). EI-MS m/z 250 (M^+, 1.5%), 249 (M^+-H, 4.5%), 248 (M^+-H_2, 23.3%), 246 (m/z 248-H_2; 100%), 200 (m/z 246- NO_2; 48.9%), 202 (m/z 248-NO_2; 8.0%), 128 ( ; 3.5%), 122 ( ; 2.2%) Anal. Calcd for $C_{10}H_{10}N_4O_2S$ C, 48.00; H, 4.00; N, 22.40; S, 12.80 Found C, 47.83; H, 4.19; N 22.13; S, 13.07.

Similarly condensation of 1-(3-aminopropyl) imidazole and 2-aminobenzothiazole with 5-nitro-2-thiophene carboxaldehyde was carried out and the crude products were purified by crystallization from methanol to give **1c**, i.e., (3-imidazol-1-yl-propyl)-(5-nitro-thiophen-2-yl-methylene)-amine and **1d**, i.e., (N-((5-nitrothiophen-2-yl)methylene)benzo[d] thiazol-2-amine).

4.2.1. Synthesis of (3-imidazol-1-yl-propyl]-(5-nitro-thiophen-2-yl methylene)-amine (1c)

Solvent of crystallization: methanol, Yield 95% m.p. 100 ^{0}C IR (KBr) ν_{max} 1626 (C=N) 1548 (Ar) cm^{-1} . ^{1}HNMR (400 MHz; DM50-d_6); δ 2.10 (m, 2H, -CH_2-), 3.50 (t, 2H, =N-CH_2-), 4.1(t, 2H, ), 6.90(s, 1H, -CH=N-), 7.20(s, 1H,

Im), 7.60(d, 1H, Th) , 7.70(s, 1H, Im), 8.10 (d, 1H, Th), 8.50(s, 1H, Im). EI-MS m/z 264 (M^+, 60.2%), 183 ( , 5.3%), 136( , 5.3%), 109 ( ; 5.7%), 95( , 100%) Anal. Calcd for $C_{11}H_{12}N_4O_2S$ C, 50.00; H, 4.54; N, 21.21; S, 12.12. Found C, 50.31; H, 4.29; N 21.09; S, 12.52.

4.2.2. Synthesis of (N-((5-nitro-thiophen-2-yl methylene)benzo[d]triozol-2-amine (1d)

Solvent of crystallization: methanol, Yield 55% m.p. 180 ^{0}C, IR (KBr) ν_{max} 1570 (C=N), 1534 and 1500 (Ar) cm^{-1}. ^{1}HNMR (500 MHz DMSO-d_6); δ 7.45-7.48 (t, 1H, Ar), 7.53-7.56 (t, 1H, Ar), 7.94-7.96 (d, 1H, Ar), 8.05-8.06 (d, 1H, Th), 8.11-8.12 (d, 1H, Ar), 8.24-8.25 (d, 1H, Th), 9.44 (s, 1H, -CH=N-). TOF-MS 289.9085 (MH^+, 100%), 243.9289 (MH^+-NO_2, 5%), 242.9240 (M^+-NO_2 ,12%) Anal. Calcd for $C_{12}H_7N_3O_2S_2$ C, 49.82; H, 2.42; N, 14.53; S, 22.14 Found C, 49.88; H, 2.25; N, 14.58; S, 22.34.

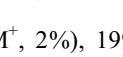
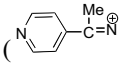
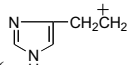
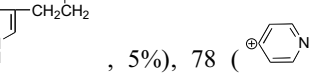
4.3. Synthesis of (N-((5-nitrothiophen-2-yl)methylene)-3-(4-(3-(5-nitrothiophen-2-yl)methylene amino)propyl)piperazin-1-yl) propan-1-amine (2a)

5-Nitro-2-thiophene carboxaldehyde (0.32 g; 2 mmol) was taken in absolute methanol (10 ml) and to it was added 1,4-bis-(3-aminopropyl)piperazine (0.20 ml; 1 mmol). The reaction contents were heated under reflux for 20 hrs and then the solvent was removed under reduced pressure. The solid product so obtained was purified by crystallization from methanol. Yield 0.140 g (30%). mp >280 ^{0}C IR(KBr) ν_{max} 1628 (C=N), 1502 (Ar) cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6); δ1.76 (m, 4H); 2.47(m, 12H); 3.59(t, 4H, 2 x CH_2-N=); 8.51 (s, 2H, 2 x –CH=N-), 8.10-8.11 (d, 2H, Th), 7.52-7.53 (d, 2H, Th),. TOF-MS 479.1615 (MH^+, 100%) . Anal. Calcd for $C_{20}H_{26}N_6O_4S_2$ C, 50.20; H, 5.43; N, 17.57; S, 13.38 Found C, 50.41; H, 5.09; N, 17.29; S, 13.01.

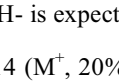
Similarly condensation of 2,4,8,10-tetraoxaspiro [5,5] undecane-3,9-dipropanamine with 5-nitro-2-thiophene carboxaldehyde using THF as the reaction solvent gave product **2b** which was purified by crystallization from THF to give pure **2b**, i.e., (5-nitro-thiophen-2-yl methylene)-[3-(9-{-[5-nitrothiophen-2-yl methylene)-amino]-propyl}-2,4,8,10-tertaoxaspiro[5,5] undec-3-yl)-propyl]-amine in 90% yield m.p.110^{0}C, IR(KBr)ν_{max} 1632 (C=N), 1509 (Ar) cm^{-1}. ^{1}HNMR (300 MHz; $CDCl_3$) δ 1.66-1.72 (m, 4H), 1.77-1.84 (m, 4H), 3.34-3.37 (d, 2H, 2 x -CH<), 3.52-3.64 (m, 8H), 4.49-4.55 (m, 4H), 7.17-7.18 (d, 2H, Th), 7.85-7.86 (d, 2H, Th), 8.20 (m, 2H, 2 x –CH=N-). FAB-MS m/z 553 (MH^+, 100%), Found mass 553.1422. Calculated for $C_{23}H_{29}N_4O_8S_2$ 553.1427 $(M + H)^+$. Anal. Calcd for $C_{23}H_{28}N_4O_8S_2$ C, 50.00; H, 5.07; N, 10.14; S, 11.59. Found C, 49.82; H, 4.98; N 9.89; S, 11.16.

Condensation of 3,5-diamino-1,2,4-triazole with 5-nitro-2- thiophene carboxaldehyde using methanol as the reaction solvent and refluxing for 10 hours gave product **2c**, which was purified by crystallization from methanol to give pure **2c**, i.e., N^3, N^5-bis-(5-nitro-thiophen-2-yl methylene)-1H-[1,2,4]-triazole-3,5-diamine in 60% yield, m.p.260 ^{0}C, IR (KBr)ν_{max} 3333 (-NH-), 1601 (C=N), 1505 (Ar) cm^{-1}. ^{1}HNMR (400 MHz; DMSO-d_6 + $CDCl_3$) δ 7.66 (bs, 2H, Ar), 8.00-8.01 (d, 2H, Ar), 9.33 (s, 2H, 2 x –CH=N-); 14.31 (s, 1H, NH, exch.), FAB-MS m/z 378 (MH^+, 10%). Anal. Calcd for $C_{12}H_7N_7O_4S_2$ C, 38.19; H, 1.85; N, 25.99; S, 16.97. Found C, 38.44; H, 1.63; N 26.21, S, 16.73

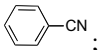
4.4. Synthesis of 2-(1H-imidazol-4-yl)-N-(1-(pyridin-yl)ethylidene)ethanamine (3a)

4-(2-Ethylamino)-1H-imidazole (0.222g; 2 mmol) was taken in absolute methanol (20 ml) and to it was added 4-acetylpyridine (0.25 ml; 2 mmol). The reaction contents were heated under reflux for 10 hours and then the solvent was removed under reduced pressure to give a crude product, which was purified by column chromatography over silica gel. Elution with ethyl acetate: methanol (7 : 3) gave pure product **3a** .Yield 0.235 g (55%). m.p 200 ^{0}C, IR (KBr) ν_{max} 3235 (-NH-), 1599 (C=N), 1493 (Ar) cm^{-1}. ^{1}HNMR (300 MHz; DMSO-d_6) δ 1.50 (s, 3H, CH_3), 2.33-2.47 (m, 2H, -CH_2-), 2.58-2.62 (m, 1H, one H of –CH_2-), 2.96-3.01(q, 1H, one H of CH_2), 7.42-7.43 (d, 2H, Py), 7.55 (s, 1H, Ar), 8.38-8.39 (d, 2H, Py), 11.50 (bs, 1H, NH, exch.) EI-MS m/z 214 (M^+, 2%), 199 (M^+-CH_3, 100%), 136 (M^+-  , 70%), 119 ( , 3%), 104 (, 2%), 95 ( , 5%), 78 ( , 2%). Anal. Calcd for $C_{12}H_{14}N_4$ C, 67.28; H, 6.54; N, 26.16; Found C, 66.87; H, 6.57; N 25.81.

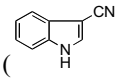
4.5. Synthesis of 2-(1H-imidazol-4-yl)-N-(1-(pyridine-2-yl)-ethylidene) ethanamine (3b)

4-(2-Ethylamino)-1H-imidazole (0.222 g; 2 mmol) and 2-acetyl pyridine (0.26 ml; 2 mmol) were taken in a round bottom flask and heated on an oil bath maintained at 120^{o}C for two hours and then cooled. The solid product was washed with pet. Ether and then crystallized from methanol to give pure product **3b**. Yield 0.175g (40%). m.p. 100 ^{0}C IR (KBr) ν_{max} 3216 (-NH-), 1656 (C=N), 1589 (Ar) cm^{-1}. ^{1}HNMR (400 MHz; DMSO-d_6) δ 1.52 (s, 3H, CH_3), 2.33-2.36 (d, 1H, one H of CH_2), 2.51-2.61 (m, 2H, -CH_2-), 2.92-2.94 (d, 1H, one H of -CH_2-), 7.16-7.19 (t, 1H, Py), 7.34-7.36 (d, 1H, Py), 7.47 (s, 1H, Ar), 7.65 (t, 1H, Py), 8.50-8.51 (d, 1H, Py) –NH- is expected downfield. FAB-MS m/z 215 (MH^+, 100%), 214 (M^+, 20%), 199 (M^+-CH_3, 6%), 136 (M^+-  ; 20%). Anal. Calcd for $C_{12}H_{14}N_4$ C, 67.28; H, 6.54; N, 26.16; Found C, 67.35; H, 6.93; N 26.53.

Similarly 4-cyanobenzaldehyde was condensed with 4-(2-ethylamino)-1H-imidazole and the crude product was purified by column chromatography over silica gel. Elution with $CHCl_3$: MeOH (19 : 1) gave pure product **3c**, i.e., 4-(1-(2-(1H-imidazol-4-yl)ethylamino)ethyl) benzonitrile in 25% yield. m.p. 185 ^{0}C IR (KBr) ν_{max} 3433 (-NH-), 2221 (C≡N), 1668(C=N), 1602 and 1486(Ar) cm^{-1}. ^{1}HNMR (300 MHz; DMSO-d_6) δ 1.66 (s, 3H, CH_3), 2.48-2.54 (q, 1H, one H of

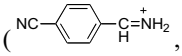
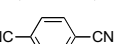
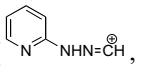
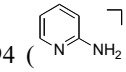
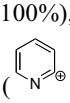
CH_2), 2.62-2.77 (m, 2H, -CH_2-), 3.12-3.18 (q, 1H, one H of -CH_2-), 7.51-7.56 (s+d, 3H, 2H Ar and 1H imidazole), 7.73-7.76 (d, 1H, Ar), 11.5 (bs, 1H, NH, exch). FAB-MS m/z 239 (MH^+, 100%), 223 (M^+-CH_3 , 20%), 136 (M^+-  ; 80%). Anal. Calcd for $C_{14}H_{14}N_4$ C, 70.58; H, 5.88; N, 23.52; Found C, 70.15; H, 5.75; N 23.86.

4.6. Synthesis of 1-((1H-indol-3-yl)methylene)-2-(pyridine-2-yl)hydrazine (4a)

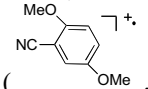
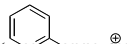
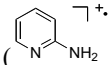
2-Hydrazino pyridine (0.109 g; 1 mmol) was taken in methanol (10 ml) and to it was added indole-3-carboxalehyde (0.145 gm; 1 mmol). The reaction contents were heated under reflux for four hours and then the solvent was removed under reduced pressure to give a crude product **4a**, which was purified by crystallization from methanol to give pure product **4a**. Yield 0. 200 g (85%). m.p. 180 ^{0}C IR (KBr) ν_{max} 3168 (NH) 1634 (C=N), 1575 and 1497 (Ar) cm^{-1}. ^{1}HNMR (500 MHz DMSO-d_6) δ 7.15-7.24 (m, 4H, Ar), 7.50-7.51 (d, 2H, Ar), 8.07-8.09 (d, 2H, Ar), 8.24 (s, 2H, -CH=N- + 1H of indole), 9.93 (s, 1H, NH, exch.), 12.12 (s, 1H, NH, exch.). GC-MS m/z 236 (M^+, 13.05%), 235 (M^+-H, 2.72%), 142 ( , 9.83%), 116 ( , 5.95%), 94 (, 100%), 78 ( , 5.87%). Anal. Calcd for $C_{14}H_{12}N_4$ C, 71.18; H, 5.08; N, 23.72; Found C, 71.03; H, 4.98; N, 23.56.

Similarly, compounds 1-(4-cyanobenzylidene)-2-(pyridine-2-yl)hydrazine (**4b**); 1-(2,5-dimethoxybenzylidene)-2-(pyridine-2-yl)hydrazine (**4c**); 1-(pyridine-2-yl)-2-(benzonitrile-4-yl) ethylidene) hydrazine (**4d**) and 1-(pyridine-2-yl)-2-(1-(pyridine-4-yl)ethylidene)hydrazine (**4e**) were synthesized in 70%, 70%, 85% and 85% yields respectively.

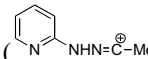
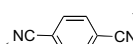
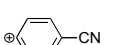
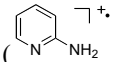
4.6.1. Synthesis of 1-(4-cyanobenzylidene)-2-(pyridine-2-yl)hydrazine (4b)

Solvent of crystallization: methanol, Yield (70%). m.p. 240 ^{0}C, IR (KBr) ν_{max} 3428 (NH) 2221 (C≡N), 1602(C=N), 1580 and 1546(Ar) cm^{-1}. ^{1}HNMR (500 MHz; DMSO-d_6) δ 6.81-6.83 (t, 1H, Ar), 7.29-7.31 (d, 1H, Ar), 7.65-7.68 (t, 1H, Ar), 7.83 (s, 4H, Ar), 8.04 (s, 1H, -CH=N-), 8.13-8.14 (d, 1H, Ar), 11.21 (s, 1H, NH, exch.) GCMS m/z 222 (M^+, 12.24%), 221 (M^+-H, 7.19%), 129 ( , 2.09%), 128( , 3.09%) 120 ( , 45.50%), 102 (, 5.26%), 94 ( , 100%), 93 ( , 11.39%), 79 ( , 13.82%), 78 ( , 9.48). Anal. Calcd for $C_{13}H_{10}N_4$ C, 70.27; H, 4.50; N, 25.22; Found C, 70.07; H, 4.29; N 25.57.

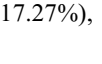
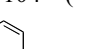
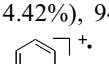
4.6.2. Synthesis of 1-(pyridine-2-yl)-2-(dimethoxybenzylidene)-2- (pyridine-2-yl) hydrazine (4c)

Solvent of crystallization: methanol, Yield 70%. m.p. 180 ^{0}C, IR (KBr) ν_{max} 3202 (NH), 1599 (C=N), 1574 and 1542 (Ar) cm^{-1}. ^{1}HNMR (500 MHz; DMSO-d_6) δ 3.76-3.79 (2s, 6H, 2 x OCH_3), 6.78 (t, 1H, Ar), 6.90-6.92 (dd, 1H, Ar), 6.99-7.01 (d, 1H, Ar), 7.22-7.23 (d, 1H, Ar), 7.43 (s, 1H, Ar), 7.67 (t, 1H, Ar), 8.08-8.09 (dd, 1H, Ar), 8.32 (s, 1H, -CH=N-), 11.02 (s, 1H, NH, exch.). GC-MS m/z 257 (M^+, 7.04%), 256 (M^+-H, 1.11%), 226 (M^+-OCH_3, 5.13), 163 ( ,2.49%), 120 ( , 14.5%), 94 ( , 100%), 93 ( , 3.57), 79 ( , 6.64%), 78 ( , 5.81%). Anal. Calcd for $C_{14}H_{15}N_3O_2$ C, 65.36; H, 5.83; N, 16.34; Found C, 65.11; H, 5.52; N 16.25.

4.6.3. Synthesis of 1-(pyridine-2-yl)-2-(benzonitrile-4-yl) ethylidene)hydrazine (4d)

Solvent of crystallization: methanol, Yield 85%. m.p. 80 ^{0}C IR(KBr) ν_{max} 3228 (NH), 2225 (-C≡N), 1688 (C=N), 1601 and 1578 (Ar) cm^{-1}. ^{1}HNMR (500 MHz; DMSO-d_6), δ 2.32 (s, 3H, -CH_3), 6.84-6.86 (t, 1H, Ar), 7.34-7.36 (d, 1H, Ar), 7.67-7.71 (t, 1H, Ar), 7.83-7.85 (d, 1H, Ar), 7.98-8.00 (d, 1H, Ar), 8.01-8.03 (d, 1H, Ar), 8.09-8.11 (d, 1H, Ar), 8.17-8.18 (d, 1H, Ar), 10.07 (s, 1H, NH, exch.). GCMS m/z 236 (M^+, 15.88%), 235 (M^+-1; 5.51%), 221 (M^+-CH_3, 100%), 134 ( , 63.33%), 128 ( , 5.83%), 102 ( , 23.18%), 94 ( , 6.19%), 93 ( , 37.67%), 79 ( , 13.53%), 78 ( , 15.34%). Anal. Calcd for $C_{14}H_{12}N_4$ C, 71.18; H, 5.08; N, 23.72; Found C, 71.53; H, 5.28; N 23.61.

4.6.4. Synthesis of 1-(pyridine-2-yl)-2-(1-(pyridine-4-yl) ethylidene) hydrazine (4e)

Solvent of crystallization: methanol, Yield 85%. m.p. 90 ^{0}C IR(KBr) ν_{max} 3253 (NH), 1600 (C=N), 1576 and 1515 (Ar). ^{1}HNMR (500 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 6.89-6.92 (t, 1H, Ar), 7.39-7.41 (d, 1H, Ar), 7.73-7.77 (t, 1H, Ar), 7.82-7.84 (d, 2H, Ar), 8.19-8.20 (d, 1H, Ar), 8.60-8.61 (d, 2H, Ar), 10.31 (s, 1H, NH, exch.) GCMS m/z 212 (M^+, 17.27%), 197 (M^+-CH_3, 92.69%), 104 ( , 4.42%), 94 ( , 6.69%), 93 ( , 45.37%), 79 ( , 15.80%), 78 ( , 32.64%). Anal. Calcd for $C_{12}H_{12}N_4$ C, 67.92; H, 5.66; N, 26.41; Found C, 67.77; H, 5.82; N 26.39.

4.7. Synthesis of N^2, N^6-bis(phenyl sulfonyl) pyridine-2,6-dicarbohydrazide (5a)

2,6-Pyridine dicarbonyl dichloride (0.204 g; 1 mmol) and benzene sulfonyl hydrazide (0.344 gm; 2 mmol) were dis-

solved in dry dichloromethane separately using 10 ml solvent in each case. Both the solutions were mixed together and allowed to stir at room temperature for twelve hours. Solid products separated out during the reaction was filtered and washed with diethyl ether. This product was then suspended in aqueous sodium carbonate solution (10%, 20 ml) and was allowed to stir for fifteen minutes and then filtered. The crude product so obtained was crystallized from methanol to give pure product **5a**. Yield 0. 380 g (80%), mp 250 ^{0}C . IR (KBr) ν_{max} 3386 and 3286 (NH), 1693 (CONH), 1541 and 1493 (Ar) cm^{-1}. ^{1}HNMR (200 MHz; DMSO-d_6) δ 7.43-7.48 (t, 2H, Ar), 7.55-7.60 (t, 3H, Ar), 7.82-7.87 (t, 1H, Ar), 7.94-7.96 (d, 6H, Ar), 8.82 (s, 2H, 2 x NH, exch.), 11.73 (s, 2H, 2 x NH, exch.) FAB-MS m/z 476 (MH$^+$, 50%). Anal. Calcd for $C_{19}H_{17}N_5O_6S_2$ C, 48.00; H, 3.57; N, 14.73; S, 13.47 Found C, 48.23; H, 3.37; N 14.53; S, 13.77.

Similarly compounds N^2, N^6-bis(tosyl) pyridine-2,6-dicarbohydrazide (**5b**) and N^2, N^6-bis(4-methoxyphenylsulfonyl) pyridine-2,6-dicarbohydrazide(**5c**) were synthesized.

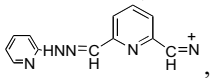
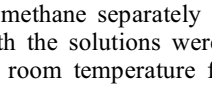
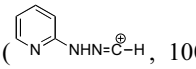
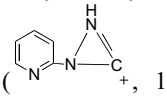
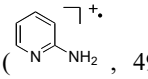
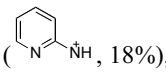
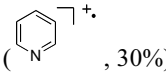
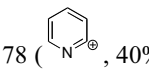
4.7.1. Synthesis of N^2, N^6-bis(tosyl) pyridine-2,6-dicarbohydrazide (5b)

Solvent of crystallization: methanol, Yield 85%. m.p. 265 ^{0}C, IR(KBr) ν_{max}3316 and 3260 (NH), 1702 (CONH), 1597 and 1537 (Ar) cm^{-1}. ^{1}HNMR (400 MHz; DMSO-d_6) δ 2.36-2.38 (2s, looking like a doublet, 6H, 2 x OCH_3), 7.31-7.34 (d, 4H, Ar), 7.39-7.41 (d, 4H, Ar), 7.69-7.71 (dd, 1H, Ar), 7.96-7.98 (d, 2H, Ar), 8.65 (s, 2H, 2 x NH-, exch.), 10.23 (s, 2H, NH, exch.) FAB-MS m/z 504 (MH$^+$, 100%). Anal. Calcd for $C_{21}H_{21}N_5O_6S_2$ C, 50.09; H, 4.17; N, 13.91; S, 12.72, Found C, 49.99; H, 3.98; N 14.30; S, 12.42.

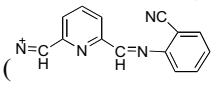
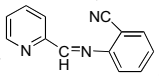
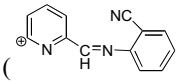
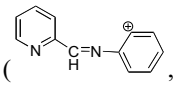
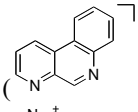
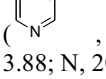
4.7.2. Synthesis of N^2, N^6-bis(4-methoxyphenyl sulfonyl) pyridine-2,6- dicarbohydrazide (5c)

Solvent of crystallization: methanol, Yield 85%. m.p. 265 ^{0}C, IR(KBr) ν_{max} 3299 and 3245 (NH), 1705 and 1679 (CONH), 1596 and 1539 (Ar)cm^{-1}. ^{1}HNMR (200 MHz, DMSO-d_6) δ 3.84 (s, 6H, 2 x OCH_3), 6.90-6.93 (d, 4H, Ar), 7.83-7.86 (d, 4H, Ar), 7.89-7.92 (t, 1H, Ar), 7.96-7.98 (d, 2H, Ar), 9.23 (s, 2H, 2 x NH, exch.), 11.58 (s, 2H, 2 x NH, exch.) FAB-MS m/z 536 (MH$^+$, 50%).Anal. Calcd for $C_{21}H_{21}N_5O_8S_2$ C, 47.10; H, 3.92; N, 13.08; S, 11.96 Found C, 47.23; H, 4.01; N 13.17; S, 12.13.

4.8. Condensation of 2,6-dialdehyde pyridine with 2-hydrazinopyridine (6)

2,6-Dialdehyde pyridine (0.135 g; 1 mmol) was taken in methanol (10 ml) and to it was added 2-hydrazinopyridine (0.220 g; 2 mmol). The reaction contents were heated under reflux for two hours and then the solvent was removed under reduced pressure to give a crude product which was purified by crystallization from THF to give pure product **6** Yield 0.270g (85%). mp 290 ^{0}C IR (KBr) ν_{max} 3201 (NH), 1601 (C=N), 1562 and 1540 (Ar). cm^{-1} ^{1}HNMR (500 MHz; DMSO-d_6) δ 6.81-6.84 (t, 2H, Ar), 7.30-7.32 (d, 2H, Ar), 7.67-7.70 (t, 2H, Ar), 7.82-7.83 (t, 1H, Ar), 7.86-7.88 (d, 2H, Ar), 8.06 (s, 2H, 2 x –CH=N-), 8.15-8.16 (d, 2H, Ar), 11.21 (s, 2H, 2 x NH, exch.). GCMS m/z (M$^+$, 12.09%), 316 (M$^+$-H, 1.77%), 224 ( , 6.84%), 198 ( , 81.92%), 197 (198-H , 15.79%), 196 (197-H, 16.53%), 120 ( , 100%), 119 (120-H, 8%), 118 ( , 10%), 94 ( , 49%), 93 ( , 18%), 79 ( , 30%), 78 ( , 40%). Anal. Calcd for $C_{17}H_{15}N_7$ C, 64.35; H, 4.73; N, 30.91; Found C, 64.17; H, 4.73; N- 31.09.

4.9. Condensation of 2,6-dialdehyde pyridine with anthranilonitrile (7)

2,6-Dialdehyde pyridine (0.135 g; 1 mmol) was taken in methanol (10 ml) and to it was added anthranilonitrile (0.236 gm; 2 mmol). The reaction contents were heated under reflux for six hours and then the solvent was removed under reduced pressure to give a crude product which was purified by crystallization from methanol to give pure product **7**. Yield 0.220 g (65%); mp 190 ^{0}C.IR(KBr) ν_{max} 2223 (C≡N), 1625 (C=N), 1577 (Ar)cm^{-1}. ^{1}HNMR (500 MHz; DMSO-d_6), δ 7.46-7.49 (t, 2H, Ar), 7.59-7.61 (d, 2H, Ar), 7.76-7.79 (t, 2H, Ar), 7.91-7.92 (d, 2H, Ar), 8.24-8.27 (q, 1H, Ar), 8.37-8.38 (d, 2H, Ar), 8.79 (s, 2H, 2 x –CH=N-). GC-MS m/z 335(M$^+$, 76.51%), 334(M$^+$-H, 21.84%), 233 ( , 68.59%), 207 ( , 34.54%), 206 ( , 68.59%), 181 ( , 10.65%), 180 ( , 14.96%),179 (m/z 180-H; 28.56%), 129 ( , 51.18%), 103 (m/z 129-CN; 20.23%), 102 ( , 100%), 79 ( , 11.20%). Anal. Calcd for $C_{21}H_{13}N_5$ C, 75.22; H, 3.88; N, 20.89; Found C, 75.52; H, 3.84; N 20.61.

4.10. Condensation of 2-hydrazinopyridine with 2,5-thiophene dialdehyde (8)

2-Hydrazino pyridine (0.218 g; 2 mmol) was taken in methanol (10 ml) and to it was added 2,5-thiophene dialdehyde (0.140 g; 1 mmol). The reaction contents were heated under reflux for 4 hrs and then the solvent was removed under reduced pressure. The crude product so obtained was crystallized from methanol to give pure product **8**. Yield 0.275 g (85%); mp 100 ^{0}C. IR (KBr) ν_{max} 3200 (NH) 1662 (C=N), 1602 and 1570 (Ar). ^{1}HNMR (500 MHz; DMSO-d_6), δ 6.81-6.86 (t, 1H, Ar), 7.13-7.17 (d, 1H, Ar), 7.41-7.42 (d, 1H, Ar), 7.66-7.69 (t, 1H, Ar), 7.94-7.95 (d, 1H, Ar), 8.13 (s, 4H, 1NH, exch. + 3H Ar), 8.20 (s, 1H, Ar), 9.87 (s, 1H, Ar),

10.03 (s, 2H, 2 x –CH=N-), 11.28 (s, 1H, NH, exch.) GC-MS m/z 322 (M^+, 2.36%). Anal. Calcd for $C_{16}H_{14}N_6S$ C, 59.62; H, 4.34; N, 26.08; S, 9.93 Found C, 59.51; H, 4.14; N 25.91; S, 10.01.

4.11. Antiinflammatory activity evaluation [25]

Antiinflammatory activity evaluation was carried out using the carrageenin induced paw oedema test in albino rats. Oedema in one of the hind paws was induced by injection of carrageenin solution (0.1 ml of 1%) into planter apponeurosis. The volume of the paw was measured plethysmographically immediately after and three hours after the injection of the irritant. The difference in volume gave the amount of oedema developed. Percent inhibition of the oedema between the control group and compound treated groups was calculated and compared with the group receiving a standard drug.

4.12. Analgesic activity evaluation [26]

Analgesia was measured by the writhing assay using Swiss mice (15-20 gm). Female mice were screened for writhing on day-1 by injecting intraperitonially 0.2 cm^3 of 0.02% aqueous solution of phenylquinone. They were kept on a flat surface and the number of writhes of each mouse was recorded for 20 min. The mice showing significant writhes (> 10) were sorted out and used for the analgesic assay on the following day. The mice consisting of 5 in each group and showing significant writhing were given orally a 25, or 50, or 100 mg/kg p.o. dose of the test compounds 15 min prior to the phenylquinone challenge. Writhing was again recorded for each mouse in a group and a percentage protection was calculated using following formula :

Protection = 100 – [{No. of writhings for treated mice)/ (No. of writhings for untreated mice)} x 100]

This was taken as a percent of analgesic response and was averaged in each group of mice. Percent of animals exhibiting analgesia was determined with each dose.

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