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# Propionic acids in organic synthesis: Novel synthesis of benzimidazole, 3,1-benzoxazine, 3-aminoquinazoline and 3-aminothieno[2,3-*d*]pyrimidine derivatives containing 2-naphthyl propionyl moiety

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Naproxenoyl chloride **2** is reacted with some nucleophilic reagents as ammonium thiocyanate and sodium azide to produce the novel isothiocyanate **3** and azide **4** derivatives, respectively. Interaction of isothiocyanate **3** with 1,2-phenylenediamine and anthranilic acid has produced the corresponding benzimidazole **5** and 3,1-benzoxazine **7** derivatives, respectively. Treatment of acid azide **4** with *p*-toluidine afforded urea derivative **9**. The novel quinazolinone **11** was synthesized by acylation of methyl anthranilate with acid chloride **2** followed by treatment with hydrazine hydrate.

**Key words**: Propionic acids, benzimidazole, benzoxazine, aminoquinazoline, aminothieno pyrimidine, naphthyl propionyl moiety, ammonium thiocyanate, sodium azide

**IPC**: **Int.Cl.[7] C 07 D**

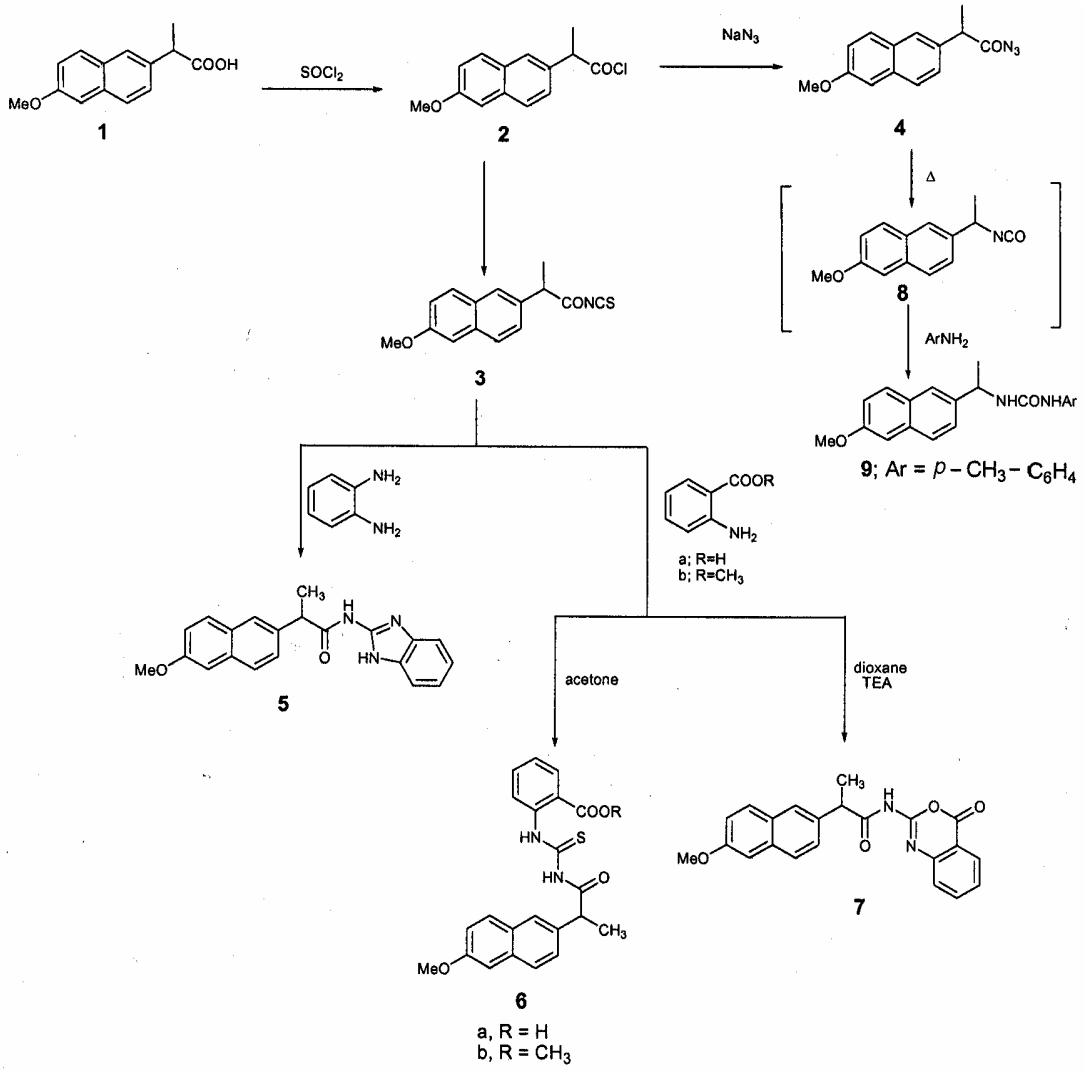
Derivatives of 2-arylpropionic acids are useful medicinal drugs having antiiflammatory activity.[1-3] Also, many quinazolines[4,5] and thieno[2,3-*d*]-pyrimidines[6,7] are known for their biological activities. In continuation of our research program[8-12] on the synthesis of novel heterocyclic compounds exhibiting biological activity, we herein report the synthesis of urea, acid azide, quinazoline and thieno[2,3-*d*]pyrimidine derivatives containing 2-naphthyl propionyl moiety.

Reaction of naproxenoyl chloride **2** with ammonium thiocyanate in acetone under reflux gave naproxenoyl isothiocyanate **3** in good yield (**Scheme I)**. The structure of the product **3** was deduced from IR spectrum which exhibited the presence of characteristic band for N=C=S functional at 2080 $cm^{-1}$. Also, compound **2** was reacted with sodium azide in refluxing acetone to furnish the novel acid azide derivative **4**. The IR spectrum showed a sharp band for $N_3$ group at 2230 $cm^{-1}$. In the present investigation the reactivity of isothiocyanate **3** towards some nucleophilic reagents was discussed. Thus, interaction of isothiocyane derivative **3** with *o*-phenylenediamine in toluene and triethylamine gave the novel benzimidazole derivative **5** ( **Scheme I**). The structure of **5** was established on the basis of analytical and spectral data. The $^1$H NMR spectrum of **5** showed the presence of a doublet at δ 1.54 for $CH_3$ group, a singlet at 3.84 for $OCH_3$ group, a quartet at 4.85 for CH, a multiplet at 7.07-7.85 for aromatic protons and two NH groups at 10.20 and 10.60 ppm. The formation of **5** was assumed to proceed via the addition of the nucleophilic group $NH_2$ to isothiocyanate **3** followed by elimination of hydrogen sulphide.[13] Also, treatment of isothiocyanate **3** with anthranilic acid and methyl anthranilate in acetone gave the thiourea derivatives **6a,b**.

On the other hand anthranilic acid underwent cyclocondensation reaction with isothiocyanate **3** in dioxane in presence of triethylamine to afford the novel 3,1-benzoxazine derivative **7**.

The novel urea derivative **9** was synthesized through reaction of **4** with *p*-toluidine under reflux in dry toluene. The formation of **9** is assumed to proceed via Curtius rearrangement[14] of acid azide **4** into isocyanate **8** followed by interaction with *p*-toluidine to form urea derivative (**Scheme I)**.

This part of the research was directed towards the synthesis of some quinazolinone derivatives containing asymmetric carbon atom in the 2- and 3- positions.




**Scheme I**

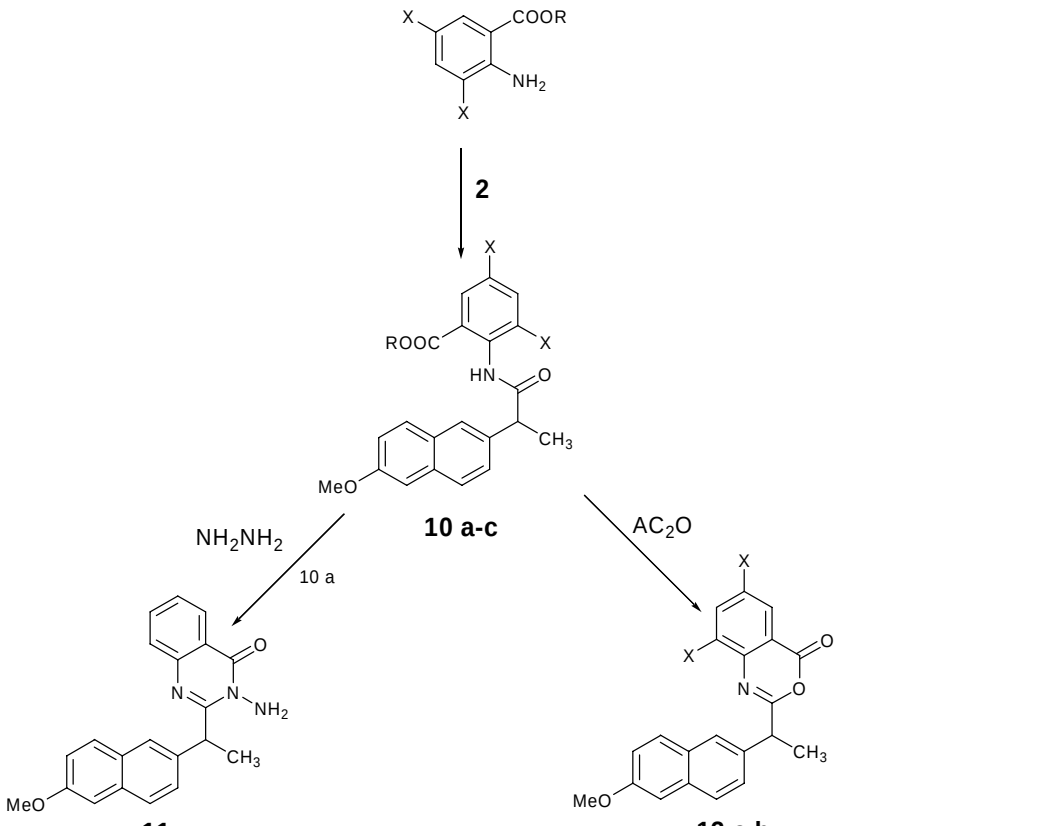
Thus, the anthranilic acid derivatives were subjected to acylation with naproxenoyl chloride **2** to yield the corresponding carboxamide derivatives **10a-c**. The amide **10a** was cyclized with hydrazine hydrate in *n*-butanol to the corresponding 3-aminoquinazolinone derivative **11**. Also, 3-aminoquinazolinone derivative **13** was obtained upon refluxing **10b,c** with acetic anhydride to form the benzoxazine derivatives **12a,b** followed by treatment of **12b** with hydrazine hydrate in *n*-butanol. In a similar manner, ethyl 4,5-disubstituted-2-aminothiophene-3-carboxylate **14a,b** were reacted with naproxenoyl chloride **2** in benzene/TEA to furnish the corresponding amide derivatives **15a,b** which on treatment with hydrazine hydrate yielded 3-aminothieno[2,3-*d*]pyrimidines **16a,b** ( **Scheme II**).

The reactivity of 3-aminoquinazolinone derivative **11** towards some carboxylic acid derivatives was studied. Thus, acylation of **11** with benzoyl chloride, chloroacetyl chloride and succinic anhydride afforded the carboxamide derivatives **17-19**. The anticipated structures were verified on the basis of elemental and spectral data.

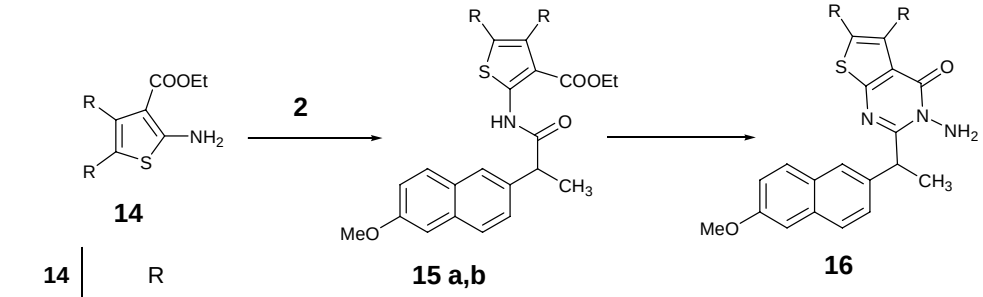
While, condensation of naproxenoyl chloride **2** with *N*-amino derivatives **20** and **21** in toluene/triethylamine afforded the novel amide derivatives **22** and **23**, respectively **(Scheme III**). The elemental analysis and spectral data supported the proposed structure.

## Experimental Section

Melting points are uncorrected. IR spectra were recorded (KBr pellet) on a Perkin-Elmer 1650 spectrometer. $^1$H NMR spectra were recorded on a Varian Gemini Spectrometer 200 (200 MHz), using

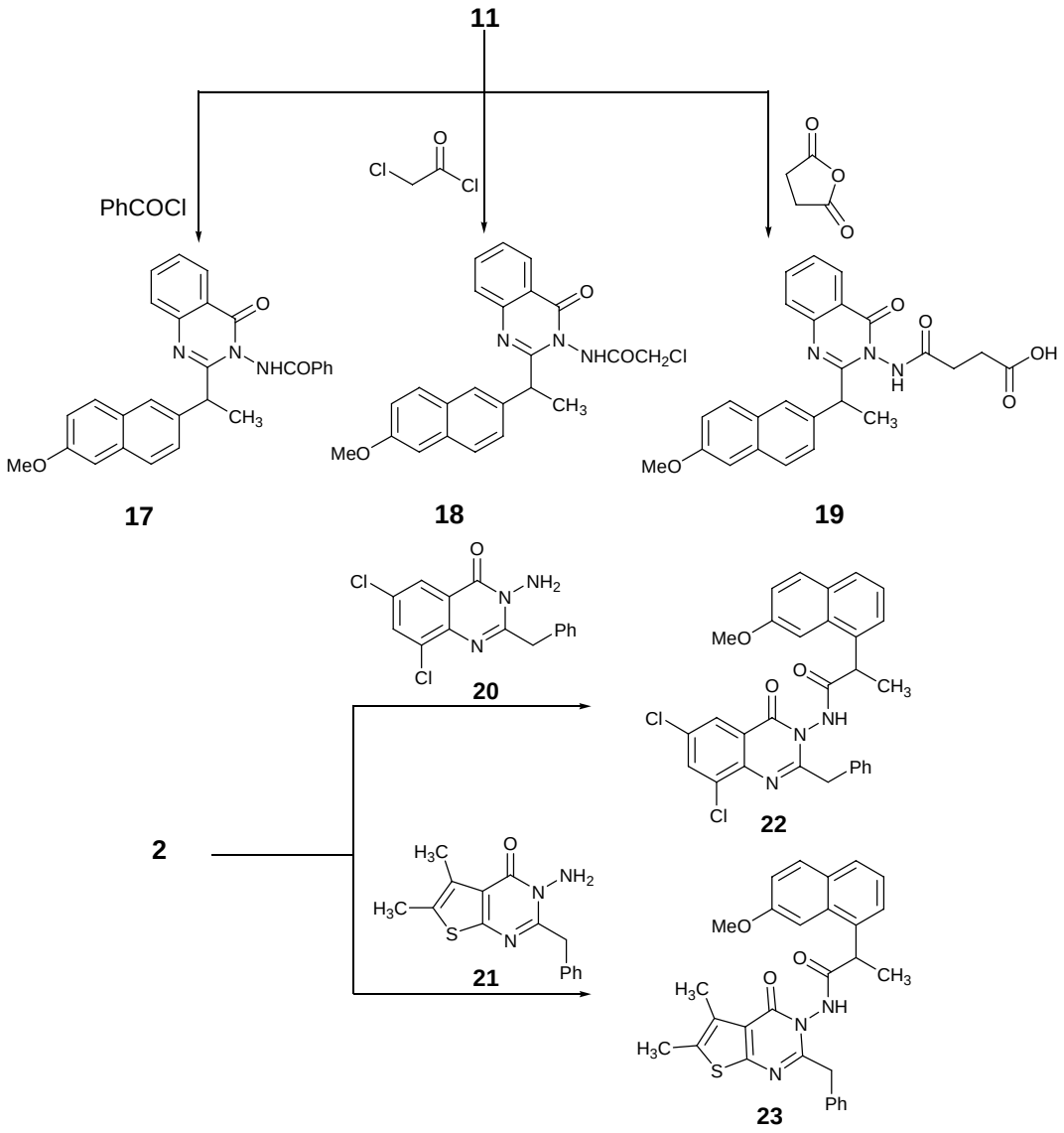



| Compd | X | R |
|---|---|---|
| **10 a** | H | $CH_3$ |
| **b** | H | H |
| **c** | Cl | H |
| **12 a** | H | - |
| **b** | Cl | - |




| **14** | R |
|---|---|
| **a** | $CH_3$ |
| **b** | $(CH_2)_4$ |

**Scheme II**




**Scheme III**

DMSO-$d_6$ as a solvent and TMS as internal standard. Chemical shifts are expressed as δ in ppm. Microanalytical data were obtained from the microanalytical data unit at the Cairo University. Physical and analytical data for the synthesized compounds are given in **Table I.**

**Naproxenoyl chloride 2**. To a solution of naproxen **1** (0.01 mole) in *m*-xylene (30 mL), $PCl_3$ (5 mL) was added. The solution was refluxed for 3 hr, cooled and the solid was filtered off, washed with ether to give **2** as colourless crystals (**Table I)**.

**2-(6-Methoxynaphthalene-2-yl) propionyliso-thiocyanate 3**. To a suspension of **2** (0.01 mole) in dry acetone (50 mL), ammonium thiocyanate (0.01 mole) was added. The reaction mixture was refluxed for 1 hr. The precipitated product was collected by filtration and recrystallized from benzene to give **3** (**Table I**).

**2-(6-Methoxynaphthalene-2-yl)propionylazide 4**. A mixture of **2** (0.01 mole) and sodium azide (0.01 mole) in dry acetone (40 mL) was refluxed for 3 hr. The precipitate that separated was filtered off, washed with ether and dried (**Table I**).

***N*-(1*H*-Benzimidazole-2-yl)-2-(6-methoxynaphthalene-2-yl)propionamide 5**. A mixture of **3** (0.01 mole) and 1,2-phenylenediamine (0.01 mole) in dry toluene (40 mL) in presence of triethylamine (0.5 mL) was refluxed for 8 hr. The hot reaction mixture was filtered, cooled and the resulting solid was dried and recrystallized from ethanol to give **5** (**Table I**). $^1$H NMR (DMSO-$d_6$): δ 1.54 (d, 3H, $CH_3$), 3.84 (s, 3H,

**Table** I — Characteristics data for the prepared compounds

| Compd | m.p. (°C) | Yield (%) | Mol. Formula (Mol.Wt) | Calcd (Found) (%) C | H | N |
|---|---|---|---|---|---|---|
| **2** | 80-82 | 75 | $C_{14}H_{13}ClO_2$ (248.5) | 67.01 (67.40 | 5.29 5.20 | -) |
| **3** | 125-26 | 65 | $C_{15}H_{13}NO_2S$ (271) | 66.42 (66.60 | 4.79 4.90 | 5.17 5.40) |
| **4** | 240-42 | 60 | $C_{14}H_{13}N_3O_2$ (255) | 65.88 (65.70 | 5.10 5.00 | 16.47 16.60) |
| **5** | 190-91 | 70 | $C_{21}H_{19}N_3O_2$ (345) | 73.04 (73.20 | 5.51 5.40 | 12.17 12.30) |
| **6a** | 130-32 | 72 | $C_{22}H_{20}N_2O_4S$ (408) | 64.71 (64.50 | 4.90 4.80 | 7.48 7.70) |
| **6b** | 165-67 | 65 | $C_{23}H_{22}N_2O_4S$ (422) | 65.40 (65.50 | 5.21 5.30 | 6.64 6.80) |
| **7** | 260-62 | 70 | $C_{22}H_{18}N_2O_4$ (374) | 70.59 (70.80 | 4.81 4.70 | 7.49 7.60) |
| **9** | 195-98 | 72 | $C_{21}H_{22}N_2O_2$ (334) | 75.45 (75.70 | 6.59 6.80 | 8.38 8.20) |
| **10a** | 100-02 | 62 | $C_{22}H_{21}NO_4$ (363) | 72.73 (72.60 | 5.79 5.90 | 3.86 3.50) |
| **10b** | 170-72 | 65 | $C_{21}H_{19}NO_4$ (349) | 72.21 (72.40 | 5.44 5.60 | 4.01 4.00) |
| **10c** | 175-77 | 68 | $C_{21}H_{17}Cl_2NO_4$ (418) | 60.29 (60.40 | 4.07 4.10 | 3.35 3.50) |
| **11** | 155-56 | 65 | $C_{21}H_{19}N_3O_2$ (345) | 73.04 (73.00 | 5.51 5.70 | 12.17 12.30) |
| **12a** | 135-36 | 65 | $C_{21}H_{17}NO_3$ (331) | 76.13 (76.10 | 5.14 5.30 | 4.23 4.50) |
| **12b** | 130-32 | 70 | $C_{21}H_{15}Cl_2NO_3$ (400) | 63.00 (63.20 | 3.75 3.80 | 3.50 3.20) |
| **13** | 260-62 | 62 | $C_{21}H_{17}Cl_2N_3O_2$ (414) | 60.87 (60.60 | 4.11 4..30 | 10.15 10.40) |
| **15a** | 115-17 | 70 | $C_{23}H_{23}NO_4S$ (411) | 67.15 (67.40 | 6.08 6.00 | 3.41 3.60) |
| **15b** | 170-72 | 66 | $C_{25}H_{27}NO_4S$ (437) | 68.65 (68.90 | 6.18 6.40 | 3.20 3.50) |
| **16a** | 185-87 | 60 | $C_{21}H_{21}N_3O_2S$ (379) | 66.49 (66.80 | 5.54 5.70 | 11.08 11.40) |
| **16b** | 220-22 | 65 | $C_{23}H_{23}N_3O_2S$ (405) | 68.15 (68.40 | 5.68 5.90 | 10.37 10.60) |
| **17** | 218-20 | 60 | $C_{28}H_{23}N_3O_3$ (449) | 74.83 (74.30 | 5.12 5.50 | 9,35 9.70) |
| **18** | 215-17 | 62 | $C_{23}H_{20}N_3O_3Cl$ (421.5) | 65.48 (65.70 | 4.75 4.60 | 9.96 9.70) |
| **19** | 250-52 | 60 | $C_{25}H_{23}N_3O_5$ (445) | 67.42 (67.70 | 5.17 5.40 | 9.44 9.80) |
| **22** | 245-46 | 65 | $C_{29}H_{23}Cl_2N_3O_3$ (532) | 65.41 (65.80 | 4.32 4.60 | 7.90 7.70) |
| **23** | 228-30 | 68 | $C_{29}H_{27}N_3O_3S$ (497) | 70.02 (70.40 | 5.43 5.60 | 8.45 8.20) |

$OCH_3$), 4.85 (q, 1H, CH), 7.07-7.85 (m, 10 H, Ar-H), 10.20, 10.60 (2s, 2H, 2NH).

**2-{3-[2-(6-Methoxynaphthalene-2-yl)propionyl]-thioureido}-benzoic acid derivatives 6a,b**. A mixture of **3** (0.01 mole) and anthranilic acid or methyl anthranilate (0.01 mole) in dry acetone (40 mL) was refluxed for 4 hr, allowed to cool, the solid product that obtained was collected by filtration and recrystallized from ethanol to give **6a,b** (**Table I**). Mass spectrum of compound **6b** exhibited a molecular ion peak at m/z 408 (35%) with base peak at m/z 94 and other peaks at m/z: 278 (25%), 265 (48%), 219 (90%), 148 (58%).

**2-(6-Methoxynaphthalene-2-yl)-*N*- (4 -oxo-4*H*-benzo[*d*][1,3]-oxazine-2-yl)propionamide 7**. A mixture of **3** (0.01 mole) and anthranilic acid or methyl anthranilate (0.01 mole) in dioxane (40 mL) and a few drops of triethylamine was refluxed for 6 hr, then allowed to cool and poured into ice-water. The solid product was collected by filtration and recrystallized from benzene to give **7** (**Table I**). Mass spectrum of compound **7** revealed a molecular ion peak at m/z 374 (60%) and base peak at 185.

**1 - [1 - (6 -Methoxynaphthalene-2-yl)-ethyl]3-(4-tolyl)urea 9**. A mixture of **4** (0.01 mole) and *p*-toluidine (0.01 mole) in dry toluene (40 mL) was heated under reflux for 1 hr. On cooling, the precipitated solid was collected by filtration and recrystallized from benzene to give **9** (**Table I**). Mass spectrum of compound **9** showed a molecular ion peak at m/z 334 (25%) with base peak at m/z 107 and other peaks at m/z: 227 (14%), 185 (68%), 141 (18%).

**2 - [2 - (6 – Methoxynaphthalene-2-yl)-propionyl amino]benzoic acid derivatives 10a-c**. A mixture of **2** (0.01 mole) and anthranilic acid derivatives in benzene (40 mL) was heated under reflux for 4 hr. The solid product was collected and recrystallized from ethanol to give **10a-c** ( **Table I**).

**3-Amino-2-[1-(6-methoxynaphthalene-2-yl)-3*H*-quinazoline-4-one 11**. A mixture of compound **10a** (0.01 mole) and hydrazine hydrate (0.12 mole) in *n*-butanol (20 mL) was heated under reflux for 10 hr. The solid product was collected and recrystallized from ethanol to give **11** (**Table I**). $^1$H NMR (DMSO-$d_6$): δ 1.66 (d, 3H, $CH_3$), 3.80 (s, 3H, $OCH_3$), 5.12 (q, 1H, CH), 5.54 (s, 2H, $NH_2$), 7.07-8.11 (m, 10H, Ar-H).

**2-[1-(6-Methoxynaphthalene-2-yl)ethyl]-benzo-[d][3,1]-oxazine-4-ones 12a,b**.

Compound **10b** or **10c** (0.01 mole) was refluxed in acetic anhydride (10 mL) for 5 hr, then allowed to

cool. The solid product was collected and recrystallized from benzene to afford **12a,b** (**Table I**).

**3-Amino-6,8-dichloro-2-[1-(6-methoxy-naphthalene-2-yl)-ethyl]-3*H*-quinazoline-4-one 13**. A mixture of **12b** (0.01 mole) and hydrazine hydrate (0.12 mole) in ethanol (50 mL) was refluxed for 24 hr and then allowed to cool. The solid product was collected and recrystallized from proper ethanol to give **13** (**Table I**). Its mass spectrum **13** showed a molecular ion peak at m/z 413 (32%) and other peaks at m/z: 414 (M+1; 32%), 226 (25%), 172 (80%), 141 (100%), 74 (30%).

**2-[2-(6-Methoxynaphthalene-2-yl)propionylamino]-thiophene-3-carboxylic acid ethyl ester 15a and 2-[2-(6-methoxynaphthalene-2-yl)propionyl-amino]-4, 5, 6, 7-tetrahydro-benzo[*b*]thiophene-3-carboxylic acid ethyl ester 15b.** A mixture of **2** (0.01 mole) and aminothiophene **14a** or **14b** (0.01 mole) in dry benzene (40 mL) in the presence of triethylamine (0.5 mL) was heated under reflux for 24 hr. The solid product was collected and recrystallized from proper ethanol to give **15a,b** (**Table I**). **15a**:$^1$H NMR: (DMSO-$d_6$): δ 1.12 (t, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 4.04 (m, 3H, CH + $CH_2O$), 7.10-7.80 (m, 6H, Ar-H), 10.87 (s, 1H, NH).

**3-Amino-2-[1-(6-methoxynaphthalene-2-yl)ethyl]-5,6-dimethyl-3*H*-thieno[2,3-*d*] pyri midine-4-one 16a and 3-amino-2-[1-(6-methoxynaphthalene-2-yl)ethyl]-5,6,7,8-tetra hydro-3*H*-benzo[4,5]thieno-[2,3-*d*]pyrimidine-4-one 16b**. A mixture of **15a** or **15b** (0.01 mole) and hydrazine hydrate (0.012 mole) in *n*-butanol (15 mL) was heated under reflux for 12 hr. The solid product was collected and recrystallized from DMF/$H_2O$ to give **16a,b**, (**Table I**). **16a**: $^1$H NMR (DMSO-$d_6$),: δ 1.63 (d, 3H, $CH_3$), 2.35, 2.38 (2s, 6H, $2CH_3$), 3.80 (s, 3H, $OCH_3$), 5.10 (q, 1H, CH), 5.56 (s, 2H, $NH_2$), 7.10-7.80 (m, 6H, Ar-H); **16b**: (KBr,$cm^{-1}$): 3400, 3300 ($NH_2$), 3050 (CH-arom), 2990 (CH-aliph), 1680 (C=O); $^1$H NMR DMSO-$d_6$: 1.48 (d, 3H, $CH_3$), 1.67, 2.48 (tetrahydrobenzo-H), 3.84 (s, 3H, $OCH_3$), 4.05 (q, 1H, CH), 4.42 (s, 2H, $NH_2$), 7.10-7.80 (m, 6H, Ar-H).

***N*-{2-[1-(6-Methoxynaphthalene-2-yl)ethyl]-4-oxo-4*H*-quinazoline-3-yl}benzamide 17** and **2-chloro-*N*-{2-[1-(6-methoxynaphthalene-2-yl)ethyl]-4-oxo-4*H*-quinazoline-3-yl}acetamide 18**. A mixture of compound **11** (0.01 mole) and benzoyl chloride or chloro acetyl chloride (0.01 mole) in pyridine (30 mL) was refluxed for 1 hr and allowed to cool and acidified with HCl. The solid product was collected and recrystallized from ethanol to give **17** and **18**, respectively. Mass spectrum of **18** displayed a molecular ion peak m/z 421 (10%) with base peak at m/z 330.

***N*-{2-[1-(6-Methoxynaphthalene-2-yl)ethyl]-4-oxo-4*H*-quinazoline-3-yl} succinamic acid 19**. A mixture of 11 (0.01mole) and succinic anhydride (0.01mole) in ethanol (30 mL) was refluxed for 3 hr and cool. The obtained product was recrystallized from benzene to afford **19** (**Table I**); $^1$H NMR (DMSO-$d_6$): δ 1.63 (d, 3H, $CH_3$), 2.75-3.0 (2t, 4H, $2CH_2$), 3.83 (s, 3H, $OCH_3$), 4.25 (q, 1H, CH), 7.1-8.1 (m, 10H, Ar-H), 10.65 (s, 1H, NH) and 10.85 (s, 1H, COOH).

***N*-(2-Benzyl-6,8-dichloro-4-oxo-4*H*-quinazoline-3-yl)-2-(6-methoxynaphthalene-2-yl)propionamide 22 and *N*-(2-benzoyl-5,6-dimethyl-4-oxo-4*H*-thieno-[2,3-*d*]pyrimidine-3-yl)-2-(6-methoxy-naphthalene-2-yl)propionamide 23**. A solution of **2** (0.01 mole) and **20** or **21** (0.01 mole) in toluene (50 mL) in the presence of triethylamine (0.5 mL) was refluxed for 48 hr. The reaction mixture was filtered, then cooled and the resulting solid was dried and recrystallized from proper solvent to give **22** and **23**, respectively (**Table I**).. Compd **22**: $^1$H NMR ( DMSO-$d_6$): δ 1.52 (d, 3H, $CH_3$), 2.17 (s, 2H, $CH_2$), 3.87 (q, 1H, CH), 3.99 (s, 3H, $OCH_3$), 7.20-8.10 (m, 13H, Ar-H), 12.85 (s, 1H, NH); **23**: $^1$H NMR (DMSO-$d_6$): δ 1.52 (d, 3H, $CH_3$), 2.47 (s, 2H, $CH_2$), 3.8 (q, 1H, CH), 3.88 (s, 3H, $OCH_3$), 7.10-7.80 (m, 11H, Ar-H), 12.39 (s, 1H, NH).

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