Arabian Journal of Chemistry (2014) 7, 900–905

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

2nd Heterocyclic Update

Synthetic utility of sydnones to couple pharmacologically important heterocycles for antitubercular activity

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Received 7 October 2010; accepted 24 January 2011
Available online 1 February 2011

KEYWORDS

Sydnone;
Synthon;
Morpholine;
Benzotriazole;
Benzothiazoilin-2-thione;
Anti-tubercular activity

Abstract In the present investigation we have utilized the 3-arylsydnones **1a–c** to couple two biodynamic moieties in amide derivatives **7–10**. The 3-arylsydnones were brominated to 4-bromo-3-arylsydnones **2a–c** which further were reacted with benzotriazole/benzothiazolin-2-thione/morpholine/diphenylamine to the corresponding final compounds. The structures of the amide derivatives were confirmed by the spectral (IR, ^{1}H NMR and Mass) and analytical data. Further, these were subjected to the antitubercular activity against *Mycobacterium tuberculae* (H37Rv). The morpholine **7a–c** and benzotriazole **8a–c** derivatives have exhibited good inhibition.

1. Introduction

Tuberculosis (TB), a highly infectious disease primarily caused by *Mycobacterium tuberculosis*, is one of the oldest recorded human afflictions and remains today a leading cause of impoverishment, human suffering and death (The Global Plan to Stop TB, 2006; Smith, 2003; Schluger, 2005; Tiruviluamala and Reichmann, 2002). It is estimated that one person in every 10 of the two billion people infected worldwide will develop infectious TB. A number of factors have led to the reduction in the successful treatment of the disease. These include a lengthy (6–9 months) multi-drug treatment program, the misuse or mismanagement of which can lead to the development of multi or extensive drug resistant TB (MDRTB or XDRTB) and the co-infection of TB with the human immunodeficiency virus (HIV) (Copp and Pearce, 2007). A new anti-TB drug needs to show the well pharmacokinetic distribution and permeation into lung tissue and cells. Furthermore, it is also desired that the novel candidate exhibits the potent bactericidal activity both against exponential and stable phase of *M. tuberculosis in vivo*. In addition, it is ideal that the novel agent possesses narrow anti-microbial spectrum specialized only against Mycobacterial species. Among the various classes of nitrogen heterocyclic compounds, secondary amines display a broad spectrum of biological activities (Rao et al., 2010).

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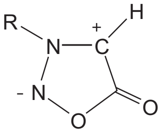
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2011.01.029

Amongst the mesoinoic compounds studied so far, sydnones have attained importance due not only to their structural features and chemical properties, but also to their biological properties. During past years many interesting data have been obtained on the structure (Cooper et al., 2005; Hasek et al., 1979), reactivities (Dumitrascu et al., 2002; Cherepanov and Kalinin, 2000), physicochemical properties (Sasaki and Ishibashi, 1990; Handa et al., 1997) and pharmacological actions (Moustafa et al., 2004; Dunkley and Thoman, 2003; Anto et al., 1994; Kier and Roche, 1967). One of the resonance hybrids of the sydnone bears a partial negative charge on the C_4 carbon. Accordingly, electrophilic substitution for instance halogenation (Tien et al., 1979), nitration (Hashimoto and Ohta, 1957), acylation (Tien and Ohta, 1972) and sulfonation (Vasileva and Yashunskii, 1958a,b) occurs at 4th position. Sydnones have played a crucial role in the development of theory in heterocyclic chemistry and have been used extensively as synthons in organic synthesis. Due to their 1,3-dipolar nature they easily undergo thermal and photochemical 1,3 dipolar cycloaddition reaction to transform into various types of heterocycles, such as 1,3,4-oxadiazole, pyrazolines, pyrazoles, phenylindazoles and tetrazines. Further, the sydnones were also used as synthons for the ring conversion into tetrahydrocarbazoles by acid hydrolysis followed by the reaction with cycloalkanones (Ohta and Kato, 1969). Resonance contributing structure responsible for such 1,3-dipolar cycloaddition is as shown below.



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This fact made us to utilize the ring conversion of 4-bromo-3-arylsydnones to the amides derivatives with biopotent secondary amines by the mild reaction.

2. Experimental

2.1. General

Melting points were determined in open capillaries. The IR spectra were recorded on a Nicolet Impact 5200 USA FT IR using KBr pellets. ^1H NMR spectra were recorded on a Bruker Varian 300-MHz FT NMR spectrometer with TMS as an internal standard. EI mass spectral analyses were recorded on a Shimadzu Japan QP2010 S model spectrometer and elemental analyses were carried out using a Heraus CHN rapid analyzer. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plate using benzene and ethyl acetate. The pharmacological evaluation was carried out at the Department of Microbiology and Immunology, NGH College of Dental sciences, Belgaum, Karnataka, India. The log *P* values have been calculated using the OSIRIS molecular property explorer software for the structural analogues of the synthesized compounds and are uncorrected. 4-Bromo-3-arylsydnone (**2a–c**) required for the present work and the title compounds were prepared according to reported methods (Kamble and Badami, 2002; Puranik and Suschitzky, 1967).

2.2. General procedure for the preparation of amide derivatives (*7*–*10*)

2.2.1. Preparation of (*7a–c*)

A mixture of 4-bromo-3-arylsydnone (**2a–c**) (0.01 mol) and secondary amine (**3**) (0.02 mol) was refluxed for 2 h at 130 °C. The progress of the reaction was followed by TLC using toluene and methanol as eluents. After completion of the reaction, the mixture was concentrated on water bath and the solid obtained was further recrystallised using ethanol to get the yellow needles of the title compound (**7a–c**).

2.2.2. Preparation of (*8–10*)

A mixture of 4-bromo-3-arylsydnone (**2a–c**) (0.01 mol) and secondary amine (**4–6**) (0.02 mol) was taken in dry ethanol and refluxed for 12 h on water bath. The progress of the reaction was followed by TLC using toluene and methanol as eluents. After completion of the reaction, the mixture was concentrated on water bath and the solid obtained was further recrystallised using ethanol to get the yellow needles of title compound (**8–10**).

*2.2.2.1. 1,2-Dimorpholino-2-(phenylamino)ethanone (**7a**).* Yield 80% m.p. 205 °C. IR (KBr): ν = 3377 (1NH), 3180 (CH aromatic), 2961 (CH aliphatic), 1610 (1C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$-d_6, 25 °C, TMS): δ = 3.32–3.39 (m, 8H, N–CH_2 morpholine ring), 3.60–3.67 (m, 8H, O–CH_2 morpholine ring), 4.45 (s, 1H, N*H*, D_2O exchangeable), 4.74 (s, 1H, C*H*), 6.43–7.04 (m, 5H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 50.1 (CH_2), 51.0 (CH_2), 71.1 (CH_2), 71.3 (CH_2), 80.8 (*C*H), 112.3, 112.5, 116.9, 129.3, 129.5, 143.5 (phenyl carbons), 169.1 (*C*=O); MS: *m*/*z* = 305 (M^+, 20), 302 (15), 291 (20), 274 (40), 264 (15), 246 (18), 231 (25), 218 (25), 205 (35), 191 (40), 179 (20), 163 (42), 147 (55), 137 (35), 123 (45), 109 (60), 100 (70), 85 (71), 83 (80), 70 (50), 57 (70), 43 (100), 41 (68), 40 (20). Anal. for $C_{16}H_{23}N_3O_3$ calcd. C 62.93, H 7.59, N, 13.76; Found C 62.90, H 7.57, N, 13.74.

*2.2.2.2. 2-(p -Tolylamino)-1,2-dimorpholinoethanone (**7b**).* Yield 75% m.p. 134 °C. IR (KBr): ν = 3360 (1NH), 3170 (CH aromatic), 2951 (CH aliphatic), 1615 (1C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$-d_6, 25 °C, TMS): δ = 2.39 (s, 3H, CH_3), 3.15–3.27 (m, 8H, N–CH_2 morpholine ring), 3.48–3.53 (d, 8H, O–CH_2 morpholine ring), 4.47 (s, 1H, N*H*, D_2O exchangeable), 4.77 (s, 1H, C*H*), 7.22–7.28 (m, 4H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 20.9 (CH_3), 50.3 (CH_2), 50.2 (CH_2), 71.1 (CH_2), 71.3 (CH_2), 80.8, 112.2, 112.5, 126.1, 130.0, 130.2, 140.5 (phenyl carbons), 169.3 (C=O); MS: *m*/*z* = 319 (M^+, 15), 317 (20), 316 (30), 302 (15), 291 (20), 274 (40), 264 (15), 246 (18), 231 (25), 218 (25), 205 (35), 191 (40), 179 (20), 163 (42), 147 (55), 137 (35), 123 (45), 109 (60), 100 (70), 85 (71), 83 (80), 70 (50), 57 (100), 43 (70), 41 (68), 40 (20). Anal. for $C_{17}H_{25}N_3O_3$ calcd. C 63.93, H 7.89, N, 13.16; Found C 63.90, H 7.87, N, 13.14.

*2.2.2.3. 2-(4-Bromophenylamino)-1,2-dimorpholinoethanone (**7c**).* Yield 86% m.p. 170 °C. IR (KBr): ν = 3408 (1NH), 3286 (CH aromatic), 2919 (CH aliphatic), 1638 (1C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$-d_6, 25 °C, TMS): δ = 3.30–3.37 (m, 8H, N–CH_2 morpholine ring), 3.62–3.65 (m, 8H, O–CH_2 morpholine ring), 4.47 (s, 1H, NH, D$_2$O exchangeable), 4.89 (s, 1H, CH), 6.32–7.26 (m, 5H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 50.1(CH_2), 51.1(CH_2), 71.1 (CH_2), 71.3(CH_2), 80.8 (CH), 111.5, 114.5, 114.7, 132.6, 132.7, 142.5 (phenyl carbons), 169.2 (C=O); MS: m/z = 385 (M^{+2}, 6), 383 (M$^+$, 20), 356 (10), 358 (10), 338 (30), 262 (30), 199 (10), 183 (40), 171 (35), 155 (65), 132 (35), 111 (30), 112 (65), 95 (40), 84 (50), 71 (52), 69 (75), 65 (70), 55 (70), 43 (100), 41 (60). Anal. for $C_{16}H_{22}BrN_3O_3$ calcd. C 50.01, H 5.77, N, 10.94; Found C 50.00, H 5.75, N, 10.95.

*2.2.2.4. 1,2-Di(1H -benzo[d][1,2,3]triazol-1-yl)-2-(phenylamino)ethanone (**8a**).* Yield 62% m.p. 181 °C. IR (KBr): v = 3360 (1NH), 3110 (CH aromatic), 2965 (CH aliphatic), 1610 (1C = O) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$-d_6, 25 °C, TMS): δ = 4.75 (s, 1H, NH, D$_2$O exchangeable), 5.69 (s, 1H, CH), 6.43–7.98 (m, 13H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 78.9 (CH), 112.3 (CH), 112.6, 116.9, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 1289.1, 129.3, 129.4, (phenyl carbons), 130.7, 133.0, 134.0, 140 (C-1,2,3 triazole), 143.5 (C-phenyl), 200.0 (C=O); MS: m/z = 420 (M$^+$, 20), 419 (20), 391 (15), 375 (40), 358 (10), 335 (15), 316 (45), 254 (45), 191 (40), 185 (40), 169 (30), 155 (40), 147 (45), 133 (40), 124 (50), 109 (48), 95 (40), 85 (55), 71 (65), 65 (60), 57 (100), 43 (70), 41 (60), 40 (20). Anal. for $C_{20}H_{15}N_7O$ calcd. C 65.03, H 4.09, N, 26.54; Found C 65.00, H 4.07, N, 26.55.

*2.2.2.5. 2-(p -Tolylamino)-1,2-di(1H-benzo[d][1,2,3]triazol-1-yl)-ethanone (**8b**).* Yield 60% m.p. 162 °C. IR (KBr): v = 3371 (1NH), 3067 (CH aromatic), 2921 (CH aliphatic), 1709 (1C=O) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$-d_6, 25 °C, TMS): δ = 2.35 (s, 3H, CH_3), 4.76 (s, 1H, NH, D$_2$O exchangeable), 5.46 (s, 1H, CH), 6.39–7.98 (m, 12H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 20.9 (CH$_3$), 78.9 (CH), 112.2 (CH), 112.4 (CH), 126.1, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 129.0, 130.0, 130.2 (phenyl carbons), 133, 134.0, 140 (C-1,2,3 triazole), 140.5 (C-phenyl carbons), 200.2 (C=O); MS: m/z = 383 (M$^+$, 15), 378 (30), 355 (25), 319 (50), 297 (20), 291 (50), 274 (25), 264 (35), 239 (55), 231 (10), 211 (25), 210 (35), 185 (35), 169 (30), 153 (15), 133 (15), 119 (20), 107 (100), 91 (80), 80 (70), 65 (30), 44 (40), 40 (10). Anal. for $C_{21}H_{17}N_7O$ calcd. C 65.79, H 4.47, N, 25.57; Found C 65.77, H 4.45, N, 25.55.

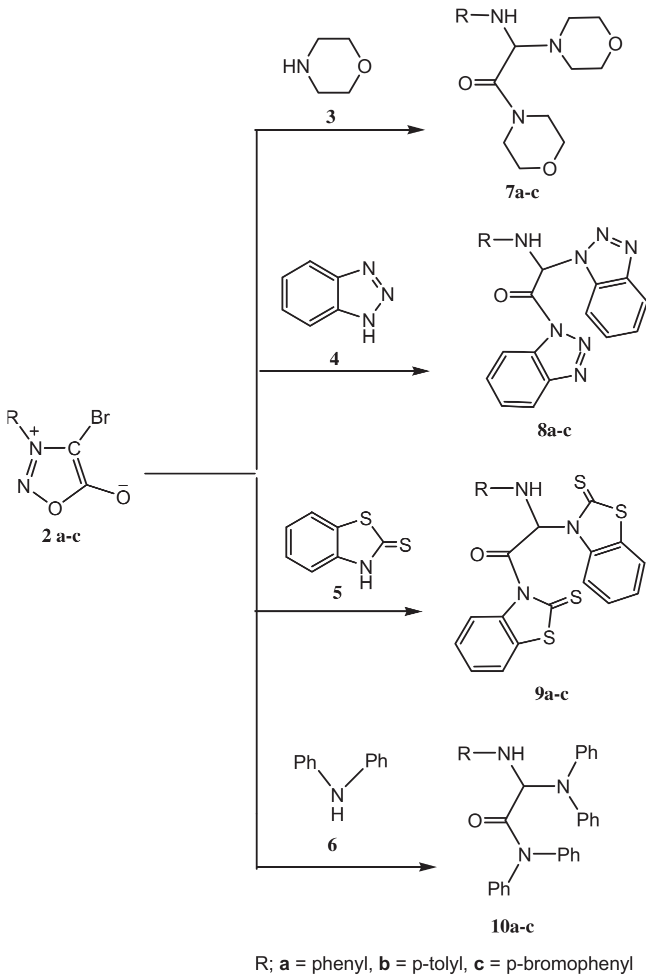
*2.2.2.6. 2-(4-Bromophenylamino)-1,2-di(1H -benzo[d][1,2,3]-triazol-1-yl)ethanone (**8c**).* Yield 69% m.p. 138 °C. IR (KBr): v = 3365 (1NH), 3113 (CH aromatic), 2962 (CH aliphatic), 1606 (1C=O) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$-d_6, 25 °C, TMS): δ = 4.72 (s, 1H, NH, D$_2$O exchangeable), 5.68 (s, 1H, CH), 7.54–7.77 (m, 12H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 78.9 (CH), 111.5, 114.5, 114.6, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.1 (phenyl carbons), 130.6 (1,2,3 triazole), 132.6, 132.7 (phenyl carbons), 133, 134.2, 140.1 (1,2,3 triazole), 142.4 (phenyl carbon), 200.1 (C=O); MS: m/z = 449 (M^{+2}, 8), 447 (M$^+$, 28), 450 (10), 420 (10) 419 (20), 391 (15), 375 (40), 358 (10), 335 (15), 316 (45), 254 (45), 191 (40), 185 (40), 169 (30), 155 (40), 147 (45), 133 (40), 124 (50), 109 (48), 95 (40), 85 (55), 71 (65), 65 (60), 57 (100), 43 (70), 41 (60), 40 (20). Anal. for $C_{20}H_{14}BrN_7O$ calcd. C 53.59, H 3.15, N, 21.87; Found C 53.57, H 3.14, N, 21.85.

*2.2.2.7. 2-(Phenylamino)-1,2-bis(2-thioxobenzo[d]thiazol-3(2H)-yl)ethanone (**9a**).* Yield 63% m.p. 190 °C. IR (KBr): v = 3365 (1NH), 3115 (CH aromatic), 2960 (CH aliphatic), 1615 (1C=O), 1470 (1C=S) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$-d_6, 25 °C, TMS): δ = 4.14 (s, 1H, NH, D$_2$O exchangeable), 4.70 (s, 1H, CH), 6.42–7.04 (m, 13H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 78.8 (CH), 112.3 (CH), 112.5 (CH), 116.9, 120.7, 124.4, 124.6, 124.8, 125.5, 125.6, 125.7, 129.3, 129.4, 129.5, 129.6, 129.8, 140.1, 141.5, 143.5 (phenyl carbons), 168.2 (amide), 193, 193.9 (thioamide); MS: m/z = 465 (M$^+$, 20), 453 (20), 435 (10), 420 (10) 419 (20), 421 (12), 408 (15), 396 (15), 381 (05), 368 (25), 354 (20), 336 (40), 332 (10), 320 (35), 306 (15), 280 (10), 274 (40), 254 (60), 249 (80), 233 (15), 218 (50), 206 (32), 193 (60), 168 (35), 167 (62), 144 (85), 139 (45), 115 (60), 105 (55), 105 (52), 91 (45), 78 (60), 63 (80), 57 (100), 43 (70), 41 (60), 40 (20). Anal. for $C_{22}H_{15}N_3OS_4$ calcd. C 56.75, H 3.25, N, 9.02; Found C 56.74, H 3.27, N, 9.00.

*2.2.2.8. 2-(p-Tolylamino)-1,2-bis(2-thioxobenzo[d]thiazol-3-(2H)-yl)ethanone (**9b**).* Yield 60% m.p. 200 °C. IR (KBr): v = 3377 (1NH), 3066 (CH aromatic), 2961 (CH aliphatic), 1610 (1C=O), 1473 (1C=S) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$-d_6, 25 °C, TMS): δ = 2.37 (s, 3H, CH_3), 4.27 (s, 1H, NH, D$_2$O exchangeable), 4.61 (s, 1H, CH), 6.60–7.48 (m, 12H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 20.9 (CH$_3$), 78.8 (CH)**,** 112.2, 112.4, 120.7, 120.9, 124.4, 124.8, 125.5, 125.6, 125.7, 126.1, 129.3, 129.4, 129.5, 130.0, 130.2, 140.1, 140.5, 141.7 (phenyl carbons), 168.2 (C=O), 193.2, 194.0 (thioamide); MS: m/z = 480 (M$^+$, 20), 466 (20), 453 (20), 435 (10), 421 (12), 408 (15), 396 (15), 381 (05), 368 (25), 354 (20), 336 (40), 332 (10), 320 (35), 306 (15), 280 (10), 274 (40), 254 (60), 249 (80), 233 (100), 218 (50), 206 (32), 193 (60), 168 (35), 167 (62), 144 (85), 139 (45), 115 (60), 105 (55), 105 (52), 91 (45), 78 (60), 63 (80), 44 (78), 41 (50), 40 (25). Anal. for $C_{23}H_{17}N_3OS_4$ calcd. C 57.59, H 3.57, N, 8.76; Found C 57.57, H 3.58, N, 8.77.

*2.2.2.9. 2-(4-Bromophenylamino)-1,2-bis(2-thioxobenzo[d] thiazol-3(2H)-yl)ethanone (**9c**).* Yield 72% m.p. 182 °C. IR (KBr): v = 3405 (1NH), 3095 (CH aromatic), 2923 (CH aliphatic), 1648 (1C=O), 1493 (1C=S) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$-d_6, 25 °C, TMS): δ = 4.40 (s, 1H, NH, D$_2$O exchangeable), 4.80 (s, 1H, CH), 6.80–7.90 (m, 12H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 78.8 (CH), 111.5, 114.5, 114.7, 120.7, 124.4, 124.6, 124.8, 125.5, 125.6, 125.8, 129.3, 129.4, 129.5, 132.6, 132.8, 140.1, 141.7, 142.5 (phenyl carbons), 168.2 (C=O), 193.2, 194.1 (thioamide); MS: m/z = 544 (M^{+2}, 7), 543 (M$^+$, 23), 514 (15) 516 (10), 510 (10), 496 (10), 481 (10), 460 (10), 439 (10), 419 (20), 391 (15), 375 (40), 358 (10), 335 (15), 305 (10), 284 (50), 269 (40), 258 (65), 242 (30), 225 (70), 211 (20), 198 (25), 183 (25), 169 (40), 167 (65), 150 (50), 136 (55), 124 (57), 127 (60), 108 (65), 90 (70), 71 (80), 57 (100), 43 (85), 41 (50), 40 (20). Anal. for $C_{22}H_{14}BrN_3OS_4$ calcd. C 48.53, H 2.59, N, 7.72; Found C 48.50, H 2.60, N, 7.70.

*2.2.2.10. 2-(Diphenylamino)-N,N-diphenyl-2-(phenylamino)-acetamide (**10a**).* Yield 57% m.p. 112 °C. IR (KBr):



Scheme 1 Formation of amide derivatives **7**–**10**.

v = 3367 (1NH), 3110 (CH aromatic), 2965 (CH aliphatic), 1610 (1C═O) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$-d_6, 25 °C, TMS): δ = 4.10 (s, 1H, NH, D$_2$O exchangeable), 4.75 (s, 1H, CH), 6.43–7.64 (m, 25H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 84.5 (CH), 112.3, 112.3, 116.9, 117.0, 117.2, 117.3, 117.4, 117.5, 117.6, 117.7, 117.9, 118.0, 118.2, 118.3, 118.5, 129.3, 129.4, 129.5, 129.6, 129.7, 129.8, 129.9, 130.0, 130.1, 130.2, 143.0, 143.1, 143.2, 143.3, 143.4 (phenyl carbons), 163.7 (C═O); MS: m/z = 469 (M$^+$, 20), 465 (10), 453 (20), 435 (10), 420 (10) 419 (20), 421 (12), 408 (15), 396 (15), 381 (05), 368 (25), 354 (20), 336 (40), 332 (10), 320 (35), 306 (15), 280 (10), 274 (40), 254 (60), 249 (80), 233 (15), 218 (50), 206 (32), 193 (60), 168 (35), 167 (62), 144 (85), 139 (45), 115 (60), 105 (55), 105 (52), 91 (45), 78 (60), 63 (80), 57 (10), 43 (100), 41 (60), 40 (20). Anal. for $C_{32}H_{27}N_3O$ calcd. C 81.85, H 5.80, N, 8.95; Found C 81.87, H 5.82, N, 8.93.

*2.2.2.11. 2-(Diphenylamino)-N,N-diphenyl-2-(p-tolylamino)-acetamide (**10b**).* Yield 50% m.p. 215 °C. IR (KBr): v = 3380 (1NH), 3060 (CH aromatic), 2965 (CH aliphatic), 1615 (1C═O) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$-d_6, 25 °C, TMS): δ = 2.36 (s, 3H, CH_3), 4.35 (s, 1H, NH, D$_2$O exchangeable), 4.74 (s, 1H, CH), 6.43–7.04 (m, 24H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 20.9 (CH$_3$), 84.5 (CH), 112.2, 112.4, 117.1, 117.2, 117.3, 117.4, 117.5, 117.6, 117.7, 117.9, 118.0, 118.1, 118.2, 118.3, 126.1, 129.4, 129.5, 129.6, 129.7, 129.8, 129.9, 130.1, 130.2, 130.3, 130.4, 140.5, 143.2, 143.4, 143.2, 143.4 (phenyl carbons), 163.9 (C═O); MS: m/z = 483 (M$^+$, 20), 455 (20), 453 (10), 435 (10), 421 (12), 408 (15), 396 (15), 381 (05), 368 (25), 354 (20), 336 (40), 332 (10), 320 (35), 306 (15), 280 (10), 274 (40), 254 (60), 249 (80), 235 (100), 218 (50), 206 (32), 193 (60), 168 (35), 167 (62), 144 (85), 139 (45), 115 (60), 105 (55), 105 (52), 91 (45), 78 (60), 63 (80), 44 (78), 41 (45), 40 (25). Anal. for $C_{33}H_{29}N_3O$ calcd. C 81.96, H 6.04, N, 8.69; Found C C 81.95, H 6.05, N, 8.67.

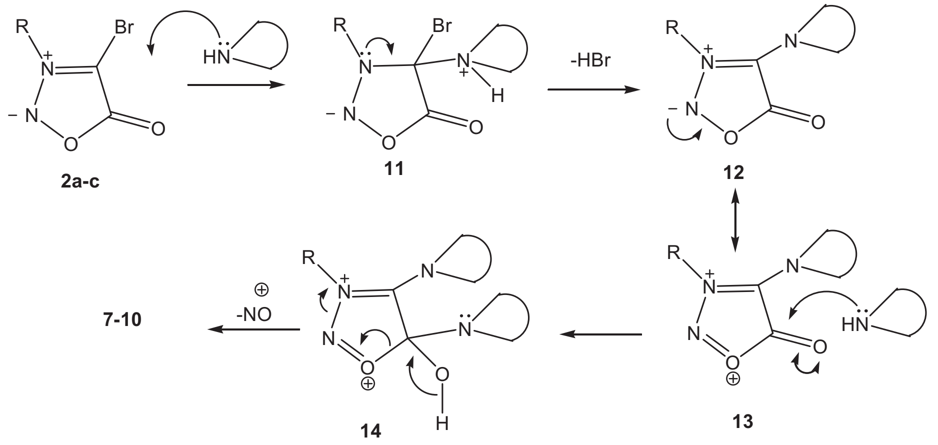
*2.2.2.12. 2-(4-Bromophenylamino)-2-(diphenylamino)-N,N-diphenylacetamide (**10c**).* Yield 59% m.p. 210 °C. IR (KBr): v = 3382 (1NH), 3090 (CH aromatic), 2921 (CH aliphatic), 1595 (1C═O) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$-d_6, 25 °C, TMS): δ = 4.40 (s, 1H, NH, D$_2$O exchangeable), 4.89 (s, 1H, CH), 6.95–7.82 (m, 24H, aromatic ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS): δ = 84.5 (CH), 111.5, 114.5, 114.7, 117.1, 117.2, 117.3, 117.4, 117.5, 117.6, 117.7, 117.8, 118.0, 118.1, 118.2, 118.3, 129.4, 129.5, 129.6, 129.7, 129.8, 129.9, 130.0, 130.3, 132.6, 132.7, 142.5, 143.2, 143.4, 143.6, 143.7 (phenyl carbons), 163.8 (C═O); MS: m/z = 549 (M^{+2}, 20), 547 (M$^+$, 10), 520 (20), 521 (10), 500 (10), 480 (20), 467 (10), 439 (12), 422 (10), 411 (10), 383 (10), 368 (12), 350 (15), 349 (20), 323 (10), 311 (10), 294 (10), 257 (15), 239 (15), 239 (10), 225 (10), 211 (12), 197 (10), 183 (30), 169 (25), 155 (30), 141 (30), 127 (40), 113 (42), 99 (50), 85 (70), 71 (80), 57 (100), 43 (82), 41 (50), 40 (15). Anal. for $C_{32}H_{26}BrN_3O$ calcd. C 70.08, H 4.78, N, 7.66; Found C 70.09, H 4.76, N, 7.68.

2.3. Anti-tubercular assay

The anti-tubercular activity of the test compounds was evaluated against the standard strain of *Mycobacterium tuberculae* H37Rv (Sahm and Washington, 1991). Antibiotic standards used were streptomycin and pyrazinamide. The procedure followed for anti-tubercular activity involves the use of Middlebrook 7H-9 broth and standard strain of *M. tuberculosis* H37Rv. The basal medium was prepared according to manufacturer's instructions (Hi-Media) and sterilized by autoclaving. Then broth (4.5 ml) was poured into each one of the sterile bottles. To this, ADC (0.5 ml) supplement was added. The supplement consists of catalase, dextrose and BSA fraction v. Then a stock solution was prepared (10 mg/ml). From this appropriate amount of solution was transferred to media bottles to achieve final concentrations of 25, 50, 100 µg/ml. Finally 10 µl suspension of *M. tuberculosis* H37Rv strain (1 lakh organisms/ml adjusted by McFarmland's turbidity standard) was transferred to each of the tubes and incubated at 37 °C. Along with this, one growth control without compound and drug controls were also set up. The bottles were inspected for growth twice a week for a period of three weeks. The appearance of turbidity indicated the growth and infers the resistance to the compound. The growth was confirmed by making a smear from each bottle and performing a ZN strain Scheme 1.

3. Results and discussion

3-Arylsydnone **1a–c** was brominated in acetic acid and the 4-bromo-3-arylsydnones (**2a–c**) formed was further reacted



Scheme 2 Proposed mechanism for the formation of amide derivatives **7**–**10**.

with the secondary amine (**3–6**) to form the title compounds (**7–10**). The proposed mechanism of the formation of the final compounds is given in Scheme 2 (Browne and Harrity, 2010). The initial attack of the first molecule of nitrogen of the amine on the C_4 carbon of the sydnone **2a–c** followed by the loss of the HBr gave an intermediate **12**. Another molecule of secondary amine attacks the carbonyl carbon atom of the resonance hybrid of **12** i.e., **13**, to form the intermediate **14** which undergoes elimination of NO^+ ion and subsequent protonation gave the final product (**7–10**). The formation of title compounds (**7–10**) was confirmed by IR, ^1H NMR, MS and elemental analyses and the data are reported in the experimental section. All these compounds have shown a common strong absorption band for NH ~ 3360–3482 cm^{-1}, CH aromatic ~ 3060–3286 cm^{-1}, CH aliphatic ~ 2919–2965 cm^{-1}, C=O ~ 1595–1709 cm^{-1}, respectively. Compounds **9a**, **9c**, **10b** have exhibited a sharp band ~1470–1493 cm^{-1}, for C=S.

The ^1H NMR spectral analysis of the title compounds exhibited the following observations. All the compounds have shown a singlet in the range 4.10–4.75 ppm. for NH proton (D_2O exchanged), down field shift for the proton CH attached to carbonyl displayed a singlet in the range 4.70–5.69 ppm, aromatic protons appeared as multiplets in the range 6.32–7.98 ppm. The compounds **7a**–**c** have shown multiplets for the methylene protons of morpholine ring in the range 3.15–3.39 ppm and 3.48–3.67 ppm, respectively. Compounds **8b**, **9b**, and **10b** have shown a singlet for methyl protons attached to phenyl ring in the range 2.35–2.37 ppm. In the electron impact studies all the compounds showed molecular ion peaks at their respective *m/z*.

3.1. Biological activity

To qualify as a drug candidate, a new molecule has to be analysed for the parameters set by Lipinski's rule (Lipinski et al., 1997) of five using Osiris property explorer. Lipinski's rule of five is a rule of thumb to evaluate drug likeliness or to determine if a compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The molecular properties are important for drug pharmacokinetics in human body, including their absorption, distribution, metabolism and excretion (ADME). The rule is important for drug development where pharmacologically active lead structure is optimized step wise for increased activity and selectivity, as well as drug like properties as described by Lipinski rule. The modification of the molecular structure often leads to drugs with higher molecular weight, more rings, more rotatable bonds and higher lipophilicity. The rule states that in general an orally active drug has not more than 5 hydrogen bond donors, and not more than 10 hydrogen acceptors, a molecular weight under 500 and the partition coefficient $c\log P$ less than 5 did not title compounds do not violate the Lipinski rule and they fall well in the range as mentioned when evaluated by the Osiris property explorer (Table 1) which lead us to evaluate the compounds experimentally. Promising results were shown for all compounds as the compounds were shown as safe drugs without any effects as mentioned in Osiris property explorer. None of the compounds were found to be tumourigenic, irritant or reproductive effect drug. Compounds (**7b**, **8b**, **9c**, and **9d**) with a methyl group on the phenyl ring have shown mutagenic effect. Rest of all the compounds has not shown any mutagenic effect. Almost all the title compounds showed $c\log P$ well within the range and also certain compounds have molecular weights less than 500. The drug likeliness ranged from −1.71 to 2.28 where as the drug score is in the range 0.1–0.82. The compounds **7a**, **7b, 10a** which have electron donating groups, such as phenyl, halogen atom and morpholine show good drug scores as depicted in Table 2. The compounds **8a–b**, **9d**, **10a–b** and **d** which have benzotriazole and diphenyl amine groups showed negative drug likeliness and as a result the drug score was less, and the presence of a halogen atom did not magnify the effect, where as the compounds **9a** and **10c** which have benzothaizoline-2-thione moiety have also shown diversified effects based on drug likeliness and drug score but $c\log P$ values are well within the range as mentioned by the rule.

In case of anti-tubercular activity studies, depicted in Table 2 the compounds with electron withdrawing atom such as bromine, heterocycles viz., morpholine and benzotriazole, (**7a**–**b**, **8a, 8c** and **10a**), have exhibited excellent inhibition (MIC) at less than or equal to 5 μg/ml concentration. The compounds with benzotriazole and diphenylamine **9d**, **10a–c** showed moderate inhibition in the range of 10–12 μg/ml. The compounds **9a–c** with benzothiazoline-2-thione showed activity only at more than 20 μg/ml concentrations as compared to standards used viz., streptomycin (7.5 μg/ml) and pyrazinamide (10 μg/ml), respectively. Encouraging activity is attributed to the pres-

Table 1 Pharmacological parameters for bioavailability of the compounds (**7**–**10**).

Entry No.	*c* log *P*	Drug likeliness	Drug score
7a	−0.09	2.23	0.90
7b	0.23	2.28	0.54
7c	0.61	1.72	0.82
8a	2.33	0.16	0.46
8b	2.65	−0.04	0.26
8c	3.03	−0.65	0.33
9a	5.52	1.70	0.27
9b	5.84	1.79	0.15
9c	6.22	1.22	0.19
10a	5.27	−1.14	0.18
10b	5.59	−1.13	0.10
10c	5.97	−1.71	0.13

Table 2 Anti-tubercular activity of the synthesized compounds (strain H37Rv[a]).

Entry No.	MIC (μg/ml)
7a	**4.5**
7b	**4.0**
7c	**3.5**
8a	**4.5**
8b	**6.0**
8c	**5.0**
9a	20
9b	25
9c	25
10a	10
10b	12
10c	12

Standard: streptomycin 7.5 μg/ml, pyrazinamide 10 μg/ml.
All compounds tested at concentration of 5, 10, 25 μg/ml.
The active compounds are marked in bold letters.

[a] ATCC number.

ence of cycloalkylating chains (e.g., morpholine ring) and with electron withdrawing substituent such as bromo appended to phenyl ring.

4. Conclusion

In conclusion, we have developed a simple and efficient method for the synthesis of novel amide derivatives incorporated with the bioactive heterocycles viz., morpholine, benzotriazole and benzothiazolin-2-thione. We also believe that the procedural simplicity, the efficiency and the easy accessibility of the reaction partners give access to a wide array of heterocyclic frameworks. The results of the anti-tubercular screening reveal that among all of the 12 compounds six compounds showed good inhibition while the other nine compounds displayed moderate to low inhibition.

Acknowledgements

The authors are thankful to the USIC for spectral IR, ^{1}H NMR, MS and CHN analyses. One of the authors (T.T.) is thankful to the UGC, New Delhi for the award of the RFSMS fellowship.

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