Synthesis and antimicrobial study of 1,2,4-triazole, quinazoline and benzothiazole derivatives from 1-naphthoylisothiocyanate

Magdy M. Hemdan*, Amin F. Fahmy and Amira A. El-Sayed

Department of Chemistry, Faculty of Science, Ain Shams University, 11566 Abbasia, Cairo, Egypt

1-Naphthoylisothiocyanate (**1**) is used as a building block in the synthesis of 1,2,4-triazole, quinazoline, benzothiazole and thiourea derivatives. The antimicrobial activity of some of the synthesised compounds was tested.

Keywords: 1-naphthoylisothiocyanate 1,2,4-triazoles, quinazolines, benzothiazoles

In view of the significant pharmacological activities associated with the derivatives of 1,2,4-triazole,[1,2] quinazoline,[3,4] and thiourea.[5,6] Our previous investigations on utilisation of aroyl isothiocyanates[7–10] afforded many different sizes heterocyclic rings. In the present work, we use 1-naphthoylisothiocyanate (**l**) and nitrogen nucleophilies as building blocks to synthesise some new derivatives of 1,2,4-triazoles, in addition, to quinazoline, benzothiazole and thiourea derivatives. We aimed to synthesise these heterocycles bearing a lipophilic naphthalene moiety (hydrocarbon moiety) in order to enhance their biological activity.

Results and discussion

The new derivatives were prepared following the reaction sequences depicted in Schemes 1 and 2. Treatment of 1-naphthoylisothiocyanate (**1**) with phenylhydrazine in acetonitrile, yielded 1,2,4-triazole derivative **2** in one-pot reaction (Scheme 1). The formation of **2** can be visualised on the basis of cyclocondensation of phenylhydrazine with isothiocyanate **1**. The structure of compound **2** was elucidated from its spectroscopic data (see experimental).

The reaction of isothiocyanate **1** with benzoylhydrazine, in acetonitrile produced the corresponding thiourea derivatives **3**. Cyclisation of compounds **3** was achieved with polyphosphoric acid (PPA) to remove a molecule of water from N-4 and benzoyl carbonyl group to give 1,2,4-triazole derivatives **4**. The spectroscopic data were consistent with the structures.

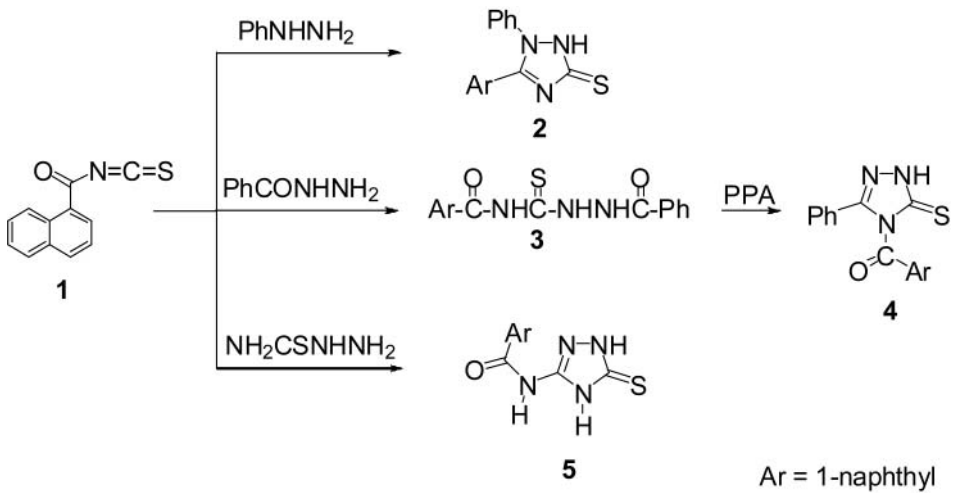
Treatment of isothiocyanate **1** with thiosemicarbazide in dry acetonitrile led to release of H_2S gas during the reaction progress, and leave a product formulated as 1,2,4-triazole derivatives **5** in one-pot reaction (Scheme 1). The formation of triazole derivative **5** can be explained on the basis of attack the amino group of thiosemicarbazide at isothiocyanato carbon atom followed by cyclisation of the non isolable intermediate thiourea derivative with removal a molecule of H_2S. The spectroscopic data correspond very well with its structure. (see Experimental).

As shown in Scheme 2, reaction of isothiocyanate **1** with anthranilic acid in acetonitrile gave thiourea derivatives **6**. Heating of compound **6** with acetic anhydride afforded quinazoline derivative **7**. The spectra of compounds **6** and **7** are consistent with their structures. The MS gave further highlight on the assigned structures of **7** since it displayed the molecular ion peaks. Unfortunately, the MS of **6** did not show the molecular ion peak, however, its MS peaks correspond very well with its proposed structure.

Refluxing of isothiocyanate **1** with 2-aminothiophenol in acetonitrile produced benzothiazole derivative **9** in a one-pot reaction. The formation of compound **9** presumably formed via cyclisation of the non isolable thiourea derivatives **8a**. However, reaction of **1** with 2-aminophenol**,** or *o*-phenylenediamine, did not give the expected benzoxazole nor benzimidazole rings, instead they afforded the corresponding thiourea derivatives **8b,c**. The spectra are consistent with these structures.

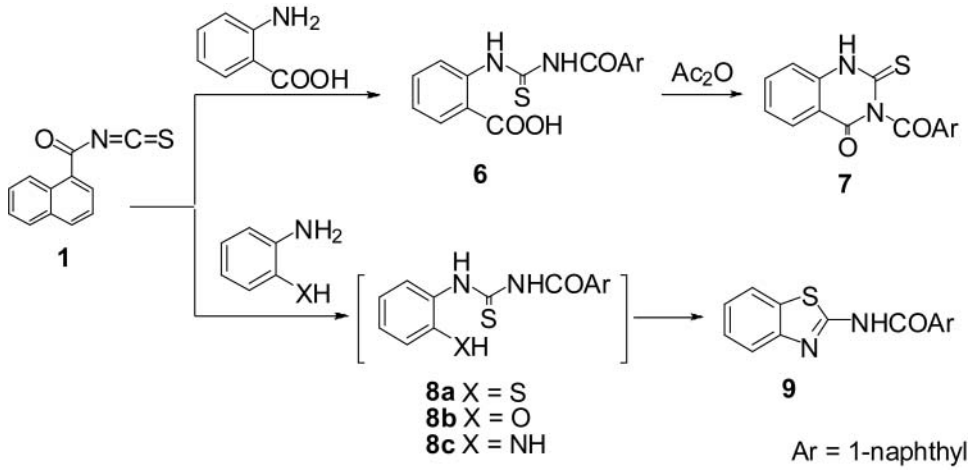
Biological activitiy

The antimicrobial screening of some of the synthesised compounds was done using the agar diffusion assay. The possible antimicrobial activities of compounds **2**, **4**, **5**, **7** and **9** were investigated to four standard organisms including the Gram-positive bacteria, *Bacillus subtilis* and, the gram-negative



Scheme 1

* Correspondent. E-mail: mhemdan39@hotmail.com



Scheme 2

Table 1 Antimicrobial activities of selected compounds

No	Inhibition zone diameter (mm/mg sample)			
	Bacillus subtills (G^+)	*Escherichia coli* (G^-)	*Candida albcans* (Fungus)	*Saccharomyces cereviseae* (Fungus)
Control DMSO	0	0	0	0
2	12	13	11	13
4	12	12	12	15
5	13	13	13	13
7	15	16	28	16
9	13	13	13	15
Tc	26	31	–	–
Am	–	–	20	20

0, no activity (inhibition zone < 7mm); weak activity (7–10 mm); moderate activity (11–15); strong activity (> 15 mm); solvent, DMSO (6 mm).

bacteria, *Esherichia coli*, in addition to pathogenic fungi *Candida albicans* and the unicellar yeast fungus *Saccharomyes cereviseae*. The obtained results presented in Table 1.

Standard discs of tetracycline (Tc) (antibacterial agent), amphotericin B (Am) (antifungal agent) served as positive controls for antimicrobial activity but filter discs impregnated with 10 μL of DMSO were used as a negative control.

Data in Table 1 emphasised the fact that the chemical agents **2**, **4**, **5**, **7** and **9** exhibited various degree of activities against Gram positive bacteria, Gram negative bacteria and fungi. Against *Bacillus subtilis* (Gram +ve rod) all the tested compounds show moderate activity (12–15 mm). For *Esherichia coli* (Gram –ve rod) all the tested compounds also show a moderate activity (12–13 mm) except compound **7** which shows strong activity (16 mm). With respect to *Candida albcans* and *Saccharomyces cereviseae* all the tested compounds show moderate activity (11–15 mm) except compound **7** which shows strong activity (28 mm) and (16 mm) respectively.

Conclusion

The introduction of hydrocarbon moiety (naphthalene moiety) to the synthesised 1,2,4-triazole, quinazoline and benzothiazole, ring systems augments the antimicrobial action appreciably. The lipophilic property of the hydrocarbon moiety, favours the permeation of the compounds through lipoid barriers in the fungal cell membrane. The greater antibacterial and antifungal activities of compound **7** than the other compounds might be attributed to its more planar and compact structure. This presumption is supported by the earlier observations that compact size and planarity of a molecule often enhance its pesticidal properties.[11,12]

Experimental

General

Melting points were determined in open capillary tubes on a Gallenkemp melting point apparatus and were uncorrected. The elemental analysis was done on Perkin-Elemer 2400 CHN elemental analyser. The IR spectra recorded on FTIR Maltson (infinity series) spectrometers as KBr discs. The ^{1}H NMR spectra were measured on Varian Gemini 300 MHz instrument with chemical shift (δ) expressed in ppm downfield from TMS as internal standard, in DMSO-d_6. Mass spectra were recorded on Shimadzu GC-MS, QP 1000 EX instrument operating at 70 eV. TLC carried out the monitoring of the progress of all reactions and homogeneity of the synthesised compounds. TLC were determined using TLC aluminum sheets silica gel F_{254} (Merck).

1-Naphthoylisothiocyanate (**1**): The of solution of 1-naphthoyl chloride (3 mmole) in dry acetonitrile (30 mL) and solid ammonium thiocyanate (3 mmole) was stirred for half an hour at room temperature.[13] The precipitated ammonium chloride was filtered off to give a clear solution of 1-naphthoyl isothiocyanate (**1**).

Reaction of isothiocyanate **1** *with the different nucleophiles; general procedure*

To a solution of isothiocyanate **1** (3 mmole) in dry acetonitrile (50 mL), phenylhydrazine, benzoyl hydrazine, thiosemicarbazide, anthranilic acid, *o*-aminothiophenol, *o*-aminophenol, or *o*-phenylenediamine, (3 mmole) was added. The reaction mixture was refluxed for 2–3 hours (TLC), cooled to room temperature. The precipitated solid was washed with ethanol, and crystallised from a suitable solvent to give the corresponding compounds.

5-(Naphthalen-1-yl)-1-phenyl-1H-1,2,4-triazole-3(2H)-thione (**2**): 85% yield; pale yellow crystals; m.p. 262–264 °C (acetic acid); IR (KBr) υ: 3111 (NH), 1553 (C=N), 1253 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 7.47 (d, J = 7.5 Hz,1H), 7.56 (d, J = 6.9 Hz, 1H), 7.60–7.70 (m, 4H), 7.99–8.18 (m, 5H), 8.70 (d, J = 8.4 Hz, 1H), 14.3 (br. s, 1NH, exchangeable with D_2O); MS (70eV) *m/z* (%): 303 (M^+, 100), 305 (M^+ +2, 8), 304 (M^++1, 23), 302 (M^+-H) (55), 243 (12), 168 (6), 153 (15), 127 (11) 91 (69), 77 (16). Anal. Calcd for $C_{18}H_{13}N_3S$ (303.38): C, 71.26; H, 4.32; N, 13.85. Found: C 71.17; H, 4.27; N, 13.78%.

N-(2-Benzoylhydrazinethiocarbonyl)-1-naphthamide (**3**): 82% yield; colorless crystals; m.p. 188–190 °C (acetic acid); IR (KBr) υ: 3295, 3198, 3100 (NH),1666 (C=O), 1166 (C=S) cm^{-1}; ^{1}H NMR (DMSO- d_6) δ: 7.43 (d, J = 6.9 Hz, 2H), 7.63–7.72 (m, 4H), 8.04–8.25 (m, 5H), 8.86 (d, J = 8.4 Hz, 1H), 9.2, 10.3, 13.3 (br. s, 3NH, exchangeable with D_2O);MS (70 eV) *m/z* (%): 349 (M^+, 9), 351(M^+ +2, 1), 350 (M^+ +1, 3), 316 (9), 213 (3), 155 (100), 127 (53), 105 (46), 77 (47). Anal. Calcd for $C_{19}H_{15}N_3O_2S$ (349.41): C, 65.31; H, 4.33; N, 12.03. Found: C, 65.23; H, 4.26; N, 11.97%.

N-(5-Thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-1-naphthamide (**5**): 86% yield; colorless crystals; m.p. > 300 °C (DMF); IR (KBr) υ: 3327, 3268, 3113 (NH)1648 (C=O), 1561 (C=N), 1144 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 7.59–7.64 (m, 3H), 7.82–7.85 (m, 3H), 8.20–8.23 (m, 1H), 6.80 (br s, 2NH, exchangeable), 12.40 (br s, 1NH, exchengeable); MS (70 eV) *m/z* (%): 270 (M^+, 6), 272 (M^+ +2, 1), 271 (M^+ +1, 1), 269 (M^+ -H) (2), 155 (100), 127 (58), 101 (3), 60 (39);).

Anal. Calcd for $C_{13}H_{10}N_4OS$ (270.31): C, 57.76; H, 3.73; N, 20.73. Found: C, 57.67; H, 3.70; N, 20.65%.

2-[3-(1-Naphthoyl)thioureido]benzoic acid (**6**): 92% yield; yellow crystals; m.p. 242–245 °C (acetic acid); IR (KBr) υ: 3300–2850 (br. OH), 3221, 3121 (NH), 1709 (C=O), 1681 (C=O), 1262 (C=S) cm^{-1}; MS (70eV) *m/z* (%): 350 ($M^{+\cdot}$, 0), 333 ($M^{+\cdot}$ –OH) (12), 198 (5), 197 (42), 171 (20), 170 (11), 137 (36), 155 (94), 127 (100), 93 (5), 77 (23), 64 (28). Anal. Calcd for $C_{19}H_{14}N_2O_3S$ (350.39): C, 65.13; H, 4.03; N, 7.99. Found: C 65.04; H, 3.97; N, 7.93.

N-(1,3-Benzothiazol-2-yl)-1-naphthamide (**9**): 79% yield; grey crystals; m.p. 164–166 °C (benzene–ethanol); IR (KBr) υ: 3176 (NH), 1681(C=O), 1549 (C=N) cm^{-1}; ^1H NMR (DMSO- d_6) δ: 7.37 (d, 1H, *J* = 7.8 Hz), 7.46–7.48 (m, 1H), 7.63–7.66 (m, 3H), 7.8 (d, 1H, *J* = 7.5 Hz), 7.93 (d, 1H, *J* = 7.2 Hz), 8.04–8.07 (m, 2H), 8.1 (d, 1H, *J* = 8.1 Hz), 8.3 (m, 1H), 12.40, (br. s, 1NH, exchangeable); MS (70 eV) *m/z* (%): 304 ($M^{+\cdot}$, 21), 305 ($M^{+\cdot}$+ 1, 6), 276 (M- CO) (21), 155 (100), 127 (90), 77 (5);). Anal. Calcd for $C_{18}H_{12}N_2OS$ (304.37): C, 71.03; H, 3.97, N, 9.20. Found: C 70.99; H, 3.93; N, 9.13.

N-(2-Hydroxyphenylthiocarbamoyl)-1-naphthamide (**8b**): 89% yield; yellow crystals; m.p. 198–190 °C (acetic acid); IR (KBr) υ: 3391 (OH), 3258, 3100 (NH),1655 (C=O), 1145 (C=S) cm^{-1}; MS (70eV) *m/z* (%): 322 ($M^{+\cdot}$, 3), 323 ($M^{+\cdot}$ + 1, 1), 305 ($M^{+\cdot}$ – OH, 0.6), 288 (7), 260 (3), 170 (5), 155 (100), 127 (61); Anal. Calcd for $C_{18}H_{14}N_2O_2S$ (322.38): C, 67.06; H, 4.38; N, 8.69. Found: C 67.14; H, 4.39; N, 8.59.

N-(2-Aminophenylthiocarbamoyl)-1-naphthamide (**8c**): 93% yield; pale yellow crystals; m.p. 208–210 °C (DMF); IR (KBr) υ: 3220, 3163 (NH), 1668 (C=O), 1151 (C=S) cm^{-1}; MS (70eV) *m/z* (%): 321 ($M^{+\cdot}$, 5), 322 ($M^{+\cdot}$ + 1, 1), 288 (11), 287 (6), 259 (7), 170 (4), 155 (100), 127 (85). Anal. Calcd for $C_{18}H_{15}N_3OS$ (321.40): C, 67.27; H, 4.70; N, 13.07. Found: C 67.33; H, 4.63; N, 12.71.

Naphthalene-1-yl(3-phenyl-5-thioxo-1,5-dihydro-4H-1,2,4-triazo-4-yl)methanone (**4**): A solution of the compound **3** (3 mmole) in glacial acetic acid (30 mL) was added to polyphosphoric acid (20 mL). The reaction mixture was heated at (150–180 °C) for 1h. Cool to room temperature; pour into ice/cold water. The precipitated solid was filtered off, and crystallised from 1,4-dioxane, 65% yield; colorless crystals; m.p. 274–276 °C; IR (KBr) υ: 3109 (NH), 1672 (C=O), 1527 (C=N), 1309 (C=S) cm^{-1}; ^1H NMR (DMSO- d_6) δ: 7.55–7.67 (m, 6H), 7.95–8.07 (m, 4H), 8.17 (d, 1H, *J* = 8.1 Hz), 8.28 (d, 1H, *J* = 7.5 Hz), 13.3, (br s, 1NH, exchangeable); MS (70eV) *m/z* (%): 331 ($M^{+\cdot}$, 16), 333 ($M^{+\cdot}$ + 2, 2), 332 ($M^{+\cdot}$ +1, 4), 330 (5), 303 (17), 155 (100), 127 (63), 77(20). Anal. Calcd for $C_{19}H_{13}N_3OS$ (331.39): C, 68.86; H, 3.95; N, 12.68. Found: C 68.80; H, 3.91; N, 12.62.

3-(l-Naphthoyl)-2-thioxo-2,3-dihydroquinazoline-4(1H)-one (**7**): A solution of compound **6** in acetic anhydride (20 mL) was heated at 90 °C for 1h. Cool, a solid product was obtained filtered off and recrystallised from dimethylformamide 79% yield; pale yellow crystals; m.p. 232–234°C; IR (KBr) υ: 3228 (NH), 1684 (C=O), 1633 (C=O), 1258 (C=S) cm^{-1}; ^1H NMR (DMSO- d_6) δ: 7.55–7.86 (m, 4H), 7.87–8.12 (m, 6H), 8.15–8.16 (m, 1H), 12.50, (br s, 1NH, exchangeable); MS (70eV) *m/z* (%): 332 ($M^{+\cdot}$, 20), 334 ($M^{+\cdot}$ + 2, 3), 333 ($M^{+\cdot}$ + 1, 4), 304 (9), 155 (100), 127(57), 77(9). Anal. Calcd for $C_{19}H_{12}N_2O_2S$ (332.38): C, 68.66; H, 3.64; N, 8.43; found C 68.58; H, 3.61; N, 8.37.

Measurement of antimicrobial activity using diffusion disc method: A filter paper sterilised disc saturated with measured quantity of the sample is placed on plate containing solid bacterial medium (nutrient agar broth) or fungal medium (Dox's medium) which have been heavily seeded with the spore suspension of the tested organism. The diameter of the clear zone of inhibition of surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism.[14]

Received 16 February 2010; accepted 22 March 2010
Paper 101007 doi: 10.3184/030823410X12707543946812
Published online: 29 April 2010

References

1 A. Cansiz, S. Servi, M. Koparir, M. Altintas and M. Digrak, *J. Chem. Soc. Pak.*, 2001, **23**, 237.
2 J.M. Kane, M.W. Dudley, S.M. Sorensen and F.P. Miller, *J. Med. Chem.*, 1988, **31**, 327.
3 P.M. Parasharya, V.C. Soni and A.R. Parikh, *J. Inst. Chem.*, 1992, **64**, 238.
4 D. Dorsch, W. Mederski, M. Osswald, P. Schelling, N. Beier, I. Lues and K. Minck, *Ger. Offen.*, *DE* 1994, **4**, 300,912; [*Chem. Abstr.*, 1994, **121**, 179608].
5 A.S. Galabov, B.S. Galabov and N.A. Neykova, *J. Med. Chem.*, 1980, **23**, 1048.
6 S. Rollas, S. Buyuktimkin and A. Cevikbas, *Arch. Pharm. (Weinheim)*, 1991, **324**, 189.
7 M.M. Hemdan, A.F. Fahmy, N.F. Ali, E. Hegazi and A. Abd-Elhaleem, *Chin. J. Chem*. 2007, **25**, 388.
8 M.M. Hemdan and M.M. El-shahawi, *J. Chem. Res.* 2009, 75.
9 M.M. Hemdan, *J. Chem. Res*. 2009, 489.
10 M.M. Hemdan, *Phosphorus, Sulfur, Silicon Relat. Elem.*, 2010, **185**, 620.
11 K. Rothwell and R.L. Wein, *Ann. Appl. Biol*. 1963, **51**, 161; [*Chem. Abstr*. 1964, **60**, 1041c].
12 L.D.S. Yadav, A.R. Misra and H. Singh, *Pestic. Sci*. 1989, **25**, 219.
13 M. Baeger, and J. Drabac, *Ger Offen* DE 1985, **3**, 504, 016; [*C.A*. 1985, **103**, 215196,].
14 M.A. Pfaller, L. Burmeister, M.A. Bartlett and M.G. Rinaldi *J. Clin. Microbiol*. 1988, **26**, 1437.