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Article

Synthesis of new *N*-Benzoxazole and *N*-Benzothiazole Derivatives of 3-(4-Substituted-phenyl)aminoisoxazol-5(2*H*)-ones and Comparison of their Base Induced Rearrangement

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3-Arilaminoisoxazol-5(2*H*)-onas, substituídas no nitrogênio com grupos benzoxazol e benzotiazol, reagem com trietilamina em etanol, sob refluxo, fornecendo os correspondentes derivados indol e imidazobenzotiazol, respectivamente.

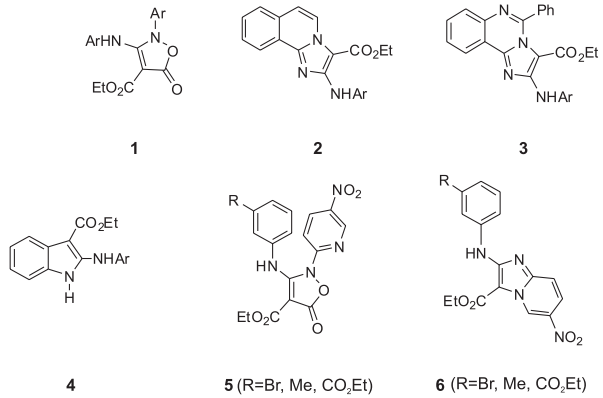
3-Arylaminoisoxazol-5(2*H*)-ones, substituted on nitrogen with benzoxazole and benzothiazole groups react with triethylamine in ethanol under reflux to afford the corresponding indole and imidazobenzothiazole derivatives, respectively.

Keywords: isoxazolones, 2-chlorobenzoxazole, 2-chlorobenzothiazole, indoles, imidazobenzothiazoles, triethylamine, base induced rearrangements

Introduction

The reaction of isoxazol-5(2*H*)-ones, unsubstituted at C-3, with base is well known[1-5] and the various intermediates have been trapped to prepare a large number of hetrocyclic system.[6-9] However, the reaction of 3-substituted compounds with base is not so well known, and the only reported reactions appear to be that described by Doleschall,[10] who alkylated the anion of ethyl 2,3-dimethyl-2,5-dihydro-5-oxo-isoxazole-4-carboxylate, in order to obtain γ-alkylated acetoacetates.

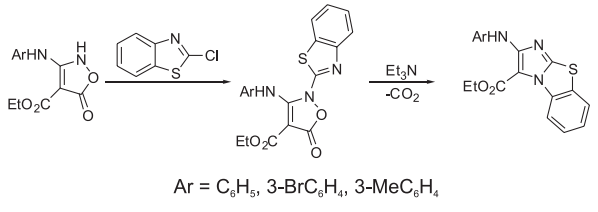
In previous studies we have shown[11] that the products obtained from the reaction of certain 2-aryl-3-arylamino-isoxazolones **1**, substituted on nitrogen with an isoquinoline or quinazoline group, react with triethylamine to give imidazoisoquinoline **2** and imidazoquinazolines **3** respectively. When the *N*-substituent is a nitropyridine, 2-aminoindole derivatives **4** are formed instead, and 2-pyridyl-3-(3-substituted phenyl)aminoisoxazol-5(2*H*)-ones **5** react with triethylamine to form the corresponding imidazo[1,2-a]pyridines **6**, an outcome that is formally the same as that achieved by photolysis or pyrolysis.[12,13]



1 **2** **3**

4 **5** (R=Br, Me, CO_2Et) **6** (R=Br, Me, CO_2Et)

We have also reported[14] that 3-arylamino-4-ethoxy-carbonylisoxazol-5(2*H*)-ones, substituted on nitrogen with a benzothiazole group, react with triethylamine to provide a convenient synthesis of ethyl 2-arylaminoimidazo[2,1-b]benzothiazole-3-carboxylates (Scheme 1).



Ar = C_6H_5, 3-BrC_6H_4, 3-MeC_6H_4

Scheme 1.

In this paper we report the synthesis of new *N*-substituted derivatives of 3-arylaminoisoxazol-5(2*H*)-ones with benzoxazole and benzothiazole substituent at nitrogen and their rearrangements in presence of triethylamine in ethanol under reflux to produce the corresponding indole and imidazobenzothiazole derivatives respectively (Scheme 2), which are suitable synthetic intermediates for a series of new hetrocycles that could be expected to have pharmaceutical applications.[17,18]

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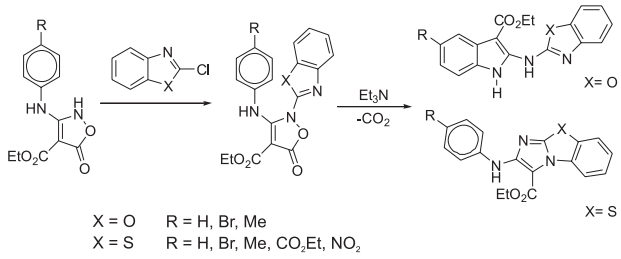
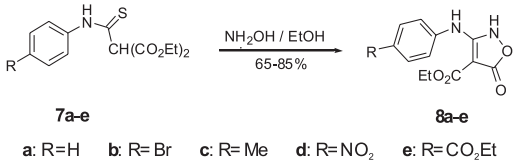


Scheme 2.

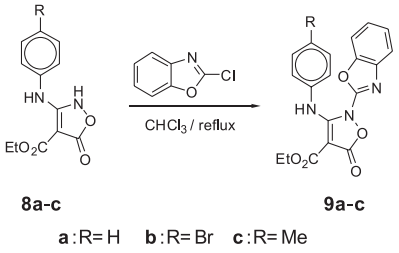
Results and Discussion

The isoxazolones **8a-e** were prepared from the reaction of the corresponding thiocarbamates **7a-e** with hydroxylamine by the general method of Worrall[15] (Scheme 3).

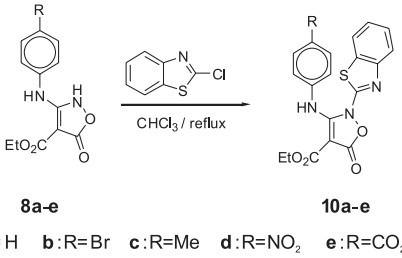


Scheme 3.

The reaction of the isoxazolones **8a-c** with 2-chlorobenzoxazole and isoxazolones **8a-e** with 2-chlorobenzothiazole in chloroform under reflux afforded the corresponding *N*-benzoxazole and *N*-benzothiazole derivatives **9a-c** (Scheme 4) and **10a-e** (Scheme 5) in good yield.

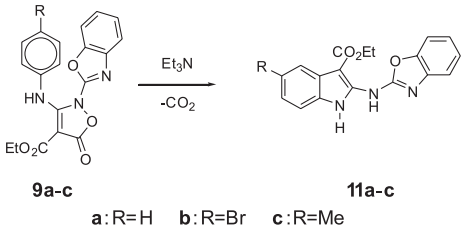


Scheme 4.



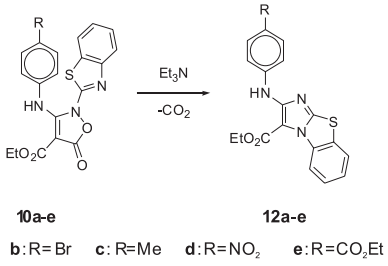
Scheme 5.

Accordingly, the reaction of the corresponding isoxazolones, substituted on nitrogen with a benzoxazole group **9a-c** with triethylamine in ethanol under reflux afforded the rearranged 2-aminoindoles **11a-c** in 41-48% (Scheme 6).



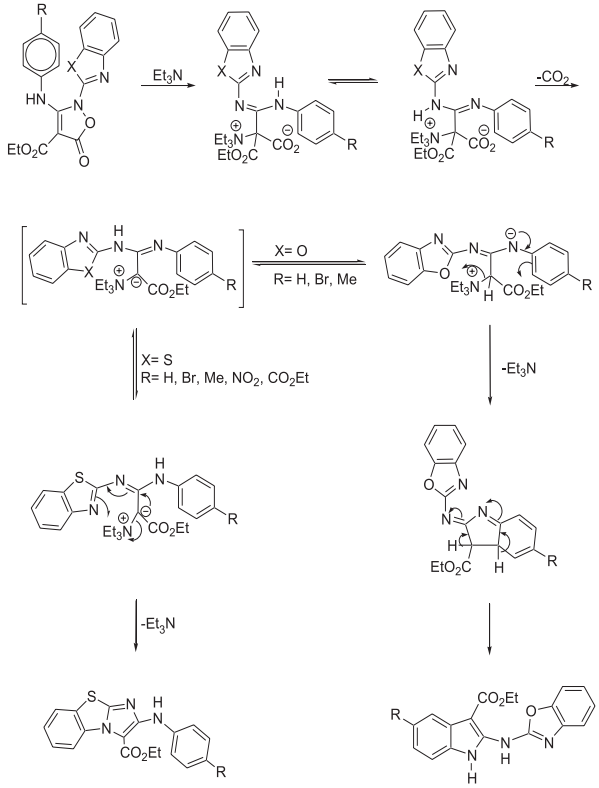
Scheme 6.

The reaction of the corresponding isoxazolones, substituted on nitrogen with a benzothiazole group **10a-e** with triethylamine in ethanol under reflux afforded the rearranged imidazobenzothiazoles **12a-e** in 40-62% (Scheme 7).



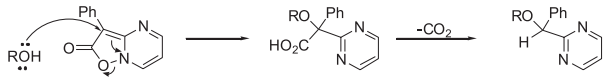
Scheme 7.

The mechanisms of rearrangements are consistent with our earlier suggestions[11,14] for the formation of indoles and imidazobenzothiazoles (Scheme 8).



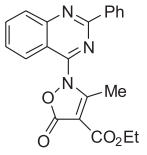
Scheme 8.

The addition of a nucleophile to C-4 of the isoxazolone has not been noted by us, but has been invoked by Zvilichovsky *et al.*[16] to rationalize the replacement of a carboxy group by an alkoxide in the isoxazolo[2,3-a]pyrimidine (Scheme 9).



Scheme 9.

However, the crucial role of arylamino group in this reaction is still not understood, as exposure of quinazoline **13** to triethylamine in refluxing ethanol led only to the recovery of unreacted starting material. Reaction under more strongly basic conditions, sodium ethoxide in ethanol, produced only 4-ethoxy-2-phenylquinazoline, but the reaction of isoxazolone **1**, substituted on nitrogen with a quinazoline group, with triethylamine afforded the corresponding imidazoquinazolin **3.**



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It is interesting that in case of benzothiazole derivative the rearrangement afforded only imidazobenzothiazoles, as shown in Scheme 2, but in case of benzoxazole derivatives, indoles are formed with no sign of any imidazobenzoxazole derivative formation, which may be due to the fact that oxygen in benzoxazole ring is more electronegative than sulphur in benzothiazole ring and therefore, the lone pair on nitrogen of benzothiazole ring is more available than that in benzoxazole ring.

Conclusions

These rearrangements therefore, appear to be generally applicable to the synthesis of heterocycles which are suitable synthetic intermediates for a series of polycylic heterocycles with possible pharmaceutical applications and could be expected to intercalate with DNA.[17,18]

Experimental

Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to Perrin and Armarego.[19] Melting points were determined on a Philip Harris C4954718 apparatus and are uncorrected. Infrared spectra were recorded on a Thermonicolet (Nexus 670) FT-infrared spectrometer, using sodium chloride cells and measured as Nujol mulls or KBr. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as the internal reference. High resolution mass spectra were recorded on a Varian Matt 311 spectrometer. Mass spectra were registered in a HP 5973 MSD connected to HP 6890 GC interfaced by a Pentium PC and relative abundances of fragments are quoted in parentheses after the *m/z* values. Microanalyses were performed on a Leco Analyzer 932.

*Ethyl 3-phenylamino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**8a**)*

In a 50 mL flask to a solution of hydroxylamine hydrochloride (4.71 g, 68 mmol) in water (20 mL), potassium bicarbonate (6.78 g, 68 mmol) was added slowly. Ethanol (80 mL) was added and the resulting potassium chloride was filtered off. Diethyl phenyl thiocarbamoylmalonate (10 g, 34 mmol) was added to the filtrate and the mixture was refluxed for 6 hours. The reaction mixture was acidified with dilute hydrochloric acid (10 mL) and the white precipitate was collected by vacuum filtration. The white solid was recrystallized from ethanol to afford the desired product (6.5 g, 78%) as white needles, mp 165-166 °C (lit.[15] 166 °C). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J* 7 Hz, 3H), 4.25 (q, *J* 7 Hz, 2H), 7.23 (m, 3H, Ar), 7.35 (m, 2H, Ar), 9.35 (bs, exchanged by D_2O addition, 2H, NH). ^{13}C NMR ($CDCl_3$) δ 13.71, 60.92, 75.82, 122.54, 127.29, 129.98, 134.83, 162.80, 164.14, 169.86. FT-IR (KBr) ν_{max}/cm^{-1}: 3358, 3119, 2990, 1748, 1665, 1583, 1327, 1025, 793.

*Ethyl 3-(4-bromophenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**8b**)*

This compound was prepared as described for (**8a**) using diethyl (4-bromophenyl) thiocarbamoylmalonate (12.71 g, 34 mmol) stirring at room temperature for 24 hours, and the white precipitate was collected by vacuum filtration. The white solid was recrystallized from acetone to afford the desired product (8.78 g, 79%) as colourless needles, mp 171-173 °C. ^{1}H NMR (DMSO-d_6) δ 1.25 (t, *J* 7.1 Hz, 3H), 4.21 (q, *J* 7.1 Hz, 2H), 7.37 (d, *J* 8.4 Hz, 2H, Ar), 7.57 (d, *J* 8.4 Hz, 2H, Ar), 8.30 (bs, exchanged by D_2O addition, 1H, NH), 9.39 (bs, exchanged by D_2O addition, 1H, NH).^{13}C NMR (DMSO-d_6) δ 15.31, 59.96, 74.69, 118.02, 125.08, 132.94, 137.10, 163.53, 164.74, 167.39. FT-IR (KBr)

ν_{max}/cm^{-1}: 3265, 2987, 2757, 1734, 1707, 1677, 1616, 1591, 1574, 1195, 1022, 797.

*Ethyl 3-(4-methylphenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**8c**)*

This compound was prepared as described for (**8a**) using diethyl (4-methylphenyl) thiocarbamoylmalonate (10.50 g, 34 mmol) and refluxing for 24 hours to afford the desired product (7.85 g, 85%) as colourless crystals, mp 164-166 °C (lit.[20] 166-168 °C). ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ 0.95 (t, *J* 7.0 Hz, 3H), 1.94 (s, 3H), 3.91 (q, *J* 7.0 Hz, 2H), 6.78 (d, *J* 9.2 Hz, 2H, Ar), 6.79 (bs, exchanged by D_2O addition, 1H, NH), 6.80 (d, *J* 9.2 Hz, 2H, Ar), 8.85 (bs, exchanged by D_2O addition, 1H, NH). ^{13}C NMR (DMSO-d_6+$CDCl_3$) δ 14.52, 20.85, 60.08, 74.69, 121.53, 130.13, 133.29, 135.64, 163.59, 165.51, 166.74. FT-IR (KBr) ν_{max}/cm^{-1}: 3409, 2976, 1708, 1619, 1572, 1072, 787. Anal. Calc. for $C_{13}H_{14}N_2O_4$: C, 55.90; H, 5.41; N, 10.03%; Found: C, 55.25; H, 5.03; N, 9.82%.

*Ethyl 3-(4-nitrophenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**8d**)*

This compound was prepared as described for (**8a**) using diethyl (4-nitrophenyl)thiocarbamoylmalonate (1.1 g, 3.23 mmol) and refluxing for 24 hours to afford the desired product (0.62 g, 65%) as yellow solid, mp 158-160 °C (lit.[20] 161-163 °C). ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ 1.30 (t, *J* 7.1 Hz, 3H), 4.36 (q, *J* 7.1 Hz, 2H), 6.32 (bs, exchanged by D_2O addition, 1H, NH), 7.51 (d, *J* 9.1 Hz, 2H, Ar), 8.23 (d, *J* 9.1 Hz, 2H, Ar), 9.53 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR (DMSO-d_6+$CDCl_3$) δ 14.43, 60.37, 76.45, 118.82, 125.33, 142.68, 143.53, 161.35, 164.74, 168.48. FT-IR (KBr) ν_{max}/cm^{-1}: 3470, 1755, 1723, 1681, 1632, 1582, 1518, 1498, 1418, 1345, 857.

*Ethyl 3-(4-ethoxycarbonylphenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**8e**)*

This compound was prepared as described for (**8a**) using diethyl (4-ethoxycarbonylphenyl)thiocarbamoylmalonate (12.48 g, 34 mmol) and refluxing for 24 hours to afford the desired product (7.07 g, 65%) as white needles, mp 126-129 °C. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ 1.38 (t, *J* 7.1 Hz, 3H), 1.40 (t, *J* 7.1 Hz, 3H), 4.35 (q, *J* 7.1 Hz, 4H), 7.34 (d, *J* 8.7 Hz, 2H, Ar), 7.55 (bs, exchanged by D_2O addition, 1H, NH), 8.04 (d, *J* 8.7 Hz, 2H, Ar), 9.58 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR (DMSO-d_6+$CDCl_3$) δ 14.29, 14.47, 60.35, 60.98, 75.69, 119.39, 126.40, 131.13, 140.52, 162.49, 165.62, 166.92. FT-IR (KBr) ν_{max}/cm^{-1}: 3278, 2984, 2761, 1716, 1683, 1601, 1575, 1278, 1184, 1104, 1021, 798. Anal. Calc. for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.00; N, 8.75%; Found: C, 55.08; H, 4.92; N, 8.92%.

*Ethyl 2-(benzoxazol-2-yl)-3-phenylamino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**9a**)*

Ethyl 3-phenylamino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**8a**) (100 mg, 0.4 mmol) and 2-chlorobenzoxazole (62 mg, 0.4 mmol) were refluxed in chloroform (5 mL) for 24 hours. The solvent was removed under reduced pressure to give colourless oil, the residue was recrystallized from ethanol to afford ethyl 2-(benzoxazol-2-yl)-3-phenylamino-5-oxo-2,5-dihydroisoxazole-4-carboxylate as white needles (51 mg, 35%), mp 114-116 °C. ^{1}H NMR ($CDCl_3$) δ 1.40 (t, *J* 7.0 Hz, 3H), 4.41 (q, *J* 7.0 Hz, 2H), 6.94 (t, *J* 7.1 Hz, 1H, Ar), 7.11 (t, *J* 7.4 Hz, 2H, Ar), 7.17 (d, *J* 7.5 Hz, 2H, Ar), 7.27 (t, *J* 7.6 Hz, 1H, Ar), 7.34 (t, *J* 7.1 Hz, 1H, Ar), 7.42 (d, *J* 8.0 Hz, 1H, Ar), 7.46 (d, *J* 7.7 Hz, 1H, Ar), 9.96 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 14.78, 61.54, 79.11, 111.26, 120.98, 122.85, 125.83, 127.26, 129.76, 135.63, 139.71, 150.04, 151.58, 164.55, 165.21. FT-IR (KBr) ν_{max}/cm^{-1}: 3270, 2990, 1784, 1668, 1628, 1489, 1201, 1030, 761, 704. GC-MS (EI, 70ev): *m/z* (%) 365 (M^+, 13), 321 [(M-CO_2), 14], 276 (32), 275 (100), 236 (32), 217 (11), 216 (62), 145 (23), 144 (82), 78 (17), 77 (76), 44 (42), 29 (58).

*Ethyl 2-(benzoxazol-2-yl)-3-(4-bromophenylamino)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**9b**)*

This compound was prepared as described for (**9a**) using the corresponding isoxazolone (**8b**) (100 mg, 0.31 mmol) and 2-chlorobenzoxazole (47 mg, 0.31 mmol) and recrystalizing from ethanol to afford the desired product as white needles (71 mg, 52%), mp 151-153 °C. ^{1}H NMR ($CDCl_3$) δ 1.45 (t, *J* 7.1 Hz, 3H), 4.44 (q, *J* 7.1 Hz, 2H), 7.11 (d, *J* 8.7 Hz, 2H, Ar), 7.30 (d, *J* 8.7 Hz, 2H, Ar), 7.36 (t, *J* 7.7 Hz, 1H, Ar), 7.42 (t, *J* 7.4 Hz, 1H, Ar), 7.51 (d, *J* 8.2 Hz, 1H, Ar), 7.54 (d, *J* 8.0 Hz, 1H, Ar), 9.99 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 14.76, 61.70, 79.68, 111.35, 120.60, 121.06, 124.30, 126.02, 127.35, 132.92, 134.97, 139.72, 150.12, 151.60, 163.61, 164.38, 165.24. FT-IR (KBr) ν_{max}/cm^{-1}: 3238, 2978, 1786, 1672, 1627, 1204, 786, 746. GC-MS (EI, 70ev): *m/z* (%) 443 [(M^+ + 2), 3], 441 (M^+, 3), 399 [(M-CO_2), 26], 397 [(M-CO_2), 26], 355 (21), 353 (21), 275 (28), 274 (95), 246 (21), 216 (36), 173 (24), 145 (33), 117 (40), 102 (30), 90 (41), 77 (37), 44 (30), 43 (68), 29 (100).

*Ethyl 2-(benzoxazol-2-yl)-3-(4-methylphenylamino)-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**9c**)*

This compound was prepared as described for (**9a**) using the corresponding isoxazolone (**8c**) (100 mg, 0.38 mmol) and 2-chlorobenzoxazole (58 mg, 0.38 mmol) and recrystalizing from ethanol to afford the desired product as white needles (61 mg, 42 %), mp 129-131 °C. ^{1}H NMR ($CDCl_3$) δ 1.45 (t, *J* 7.1 Hz, 3H), 2.12 (s, 3H), 4.45 (q, *J* 7.1 Hz, 2H), 6.92 (d, *J* 7.9 Hz, 2H, Ar), 7.08 (d, *J* 7.9 Hz, 2H, Ar), 7.33 (t, *J* 7.7 Hz, 1H, Ar), 7.40 (t, *J* 8.2 Hz, 1H, Ar), 7.47 (d, *J* 8.2 Hz, 1H, Ar), 7.53 (d, *J* 7.9 Hz, 1H, Ar), 9.90 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 14.81, 21.11, 61.50, 78.91, 111.27, 121.08, 122.94, 125.74, 127.13, 130.29, 132.99, 137.44, 139.91, 150.15, 151.76, 164.01, 164.85, 165.38. FT-IR (KBr) ν_{max}/cm^{-1}: 3267, 1790, 1683, 1667, 1632, 1561, 1514, 1356, 1293, 1201, 1030, 985, 791. GC-MS (EI, 70ev): *m/z* (%) 379 (M^+, 7), 335 [(M-CO_2), 34], 290 (23), 289 (100), 251 (11), 250 (46), 230 (57), 158 (60), 117 (55), 91 (100), 77 (44), 65 (50), 44 (9), 29 (66).

*Ethyl 2-(benzothiazol-2-yl)-3-phenylamino-5-oxo-2,5-dihydro-4-carboxylate (**10a**)*

This compound was prepared as lit.[14] procedure.

*Ethyl 2-(benzothiazol-2-yl)-3-(4-bromophenyl)amino-5-oxo-2,5-dihydro-4-carboxylate (**10b**)*

Ethyl 3-(4-bromophenyl)amino-5-oxo-2,5-dihydro-isoxazole-4-carboxylate (**8b**) (100 mg, 0.3 mmol) and 2-chloro-benzothiazole (51 mg, 0.3 mmol) were refluxed in chloroform (5 mL) for 48 hours. The solvent was removed under reduced pressure to give colourless oil, which was solidified on standing, the residue was recrystallized from ethanol to afford the desired product as white needles (74 mg, 52%), mp 172-174 °C. ^{1}H NMR ($CDCl_3$) δ 1.34 (t, *J* 6.9 Hz, 3H), 4.33 (q, *J* 6.9 Hz, 2H), 7.1 (d, *J* 8.7 Hz, 2H, Ar), 7.36 (d, *J* 8.7 Hz, 2H, Ar), 7.40 (td, *J* 7.5 Hz, *J* 1.5 Hz, 1H, Ar), 7.46 (td, *J* 7.2 Hz, *J* 1.5 Hz, 1H, Ar), 7.67 (d, *J* 7.5 Hz, 1H, Ar), 7.81 (d, *J* 7.5 Hz, 1H, Ar), 10.16 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 14.31, 61.14, 79.10, 119.70, 121.62, 122.98, 123.93, 126.03, 127.10, 132.27, 136.00, 149.08, 157.19, 161.43, 163.02, 163.94. FT-IR (KBr) ν_{max}/cm^{-1}: 3188, 2971, 1783, 1696, 1602, 1556, 1515, 1371, 1204, 764 cm^{-1}. GC-MS (EI, 70ev): *m/z* (%) 461 [(M^+ + 2), 4], 459 (M^+, 4), 417 [(M-CO_2), 31], 415 [(M-CO_2), 30], 371 (25), 369 (23), 291 (23), 290 (100), 263 (12), 262 (26), 224 (11), 177 (14), 161 (16), 135 (11), 134 (15), 108 (10), 29 (13) and HRMS *m/z* 458.98883 ($C_{19}H_{14}BrN_3O_4S$ requires 458.98884).

*Ethyl 2-(benzothiazol-2-yl)-3-(4-methylphenyl)amino-5-oxo-2,5-dihydro-4-carboxylate (**10c**)*

This compound was prepared as described for (**10b**) using the corresponding isoxazolones (**8c**) (70 mg, 0.27 mmol) and 2-chlorobenzothiazole (51 mg, 0.27 mmol) to afford the desired product as white needles (45 mg, 52%), after recrystalization from ethanol, mp 138-140 °C. ^{1}H NMR ($CDCl_3$) δ 1.35 (t, *J* 7.2 Hz, 3H), 2.31 (s, 3H), 4.27 (q, *J* 7.2 Hz, 2H), 7.00 (d, *J* 8.1 Hz, 1H, Ar), 7.07 (d, *J* 7.2 Hz, 1H, Ar), 7.27 (d, *J* 6.9 Hz, 1H, Ar), 7.30-7.52 (m, 2H, Ar), 7.69 (d, *J* 8.1 Hz, 1H, Ar), 7.87 (d, *J* 7.8 Hz, 1H, Ar), 7.93 (d, *J* 8.1 Hz, 1H, Ar), 9.21 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 14.46, 20.88, 60.47, 75.55, 121.12, 121.76, 122.53, 122.85, 125.81, 126.74, 126.93, 129.74, 130.43, 132.68, 136.45, 164.51, 165.41, 167.25. FT-IR (KBr) ν_{max}/cm^{-1}: 3218, 3075, 1979, 1778, 1708, 1573, 1448, 1390, 1201, 726.

*Ethyl 2-(benzothiazol-2-yl)-3-(4-nitrophenyl)amino-5-oxo-2,5-dihydro-4-carboxylate (**10d**)*

This compound was prepared as described for (**10b**) using the corresponding isoxazolones (**8d**) (100 mg, 0.34 mmol) and 2-chlorobenzothiazole (58 mg, 0.34 mmol) to afford the desired product as pale yellow (78 mg, 53%), after recrystalization from ethanol, mp 169-171 °C. ^{1}H NMR ($CDCl_3$) δ 1.38 (t, *J* 7.2 Hz, 3H), 4.34 (q, *J* 7.2 Hz, 2H), 7.36 (d, *J* 9.0 Hz, 2H, Ar), 7.40 (td, *J* 6.9 Hz, *J* 1.0 Hz, 1H, Ar), 7.45 (td, *J* 6.7Hz, *J* 1.0 Hz, 1H, Ar), 7.60 (dd, *J* 8.7 Hz, *J* 1.5 Hz, 1H, Ar), 7.83 (dd, *J* 8.4 Hz, *J* 1.5 Hz, 1H, Ar), 8.16 (d, *J* 9.0 Hz, 2H, Ar), 10.51 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 14.31, 61.50, 80.56, 121.45, 121.70, 122.84, 124.93, 126.18, 127.27, 132.93, 142.79, 144.83, 148.92, 157.09, 160.55, 163.78. FT-IR (KBr) ν_{max}/cm^{-1}: 3203, 3072, 2981, 1783, 1698, 1604, 1558, 1514, 1375, 1339, 760. GC-MS (EI, 70ev): *m/z* (%) 426 (M^+, 7), 382 [(M-CO_2), 86], 336 (43), 291 (26), 290 (100), 262 (41), 235 (11), 189 (16), 177 (19), 161 (41), 160 (23), 150 (26), 135 (19), 134 (39), 108 (16), 90 (24), 44 (18), 29 (25).

*Ethyl 2-(benzothiazol-2-yl)-3-(4-ethoxycarbonylphenyl) amino-5-oxo-2,5-dihydro-4-carboxylate (**10e**)*

This compound was prepared as described for (**10b**) using the corresponding isoxazolones (**8e**) (100 mg, 0.31 mmol) and 2-chlorobenzothiazole (53 mg, 0.31 mmol) to afford the desired product as white prisms (65 mg, 46%), after recrystalization from ethanol, mp 157-159 °C. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, *J* 7.0 Hz, 3H), 1.35 (t, *J* 7.0 Hz, 3H),

4.31 (q, *J* 7.0 Hz, 4H), 7.26 (d, *J* 8.4 Hz, 2H, Ar), 7.36 (d, *J* 7.2 Hz, 1H, Ar), 7.41 (d, *J* 6.6 Hz, 1H, Ar), 7.62 (d, *J* 7.8 Hz, 1H, Ar), 7.79 (d, *J* 8.1 Hz, 1H, Ar), 7.93 (d, *J* 8.4 Hz, 2H, Ar), 10.35 (s, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 14.24, 14.28, 61.13, 61.21, 79.73, 121.10, 121.61, 122.98, 127.05, 127.90, 130.73, 133.19, 140.86, 149.04, 157.21, 161.01, 162.88, 163.87, 165.48. FT-IR (KBr) ν_{max}/cm^{-1}:3448, 3072, 2980, 1801, 1713, 1689, 1602, 1574, 1384, 1276, 762.

*Ethyl 2-(benzoxazol-2-ylamino)-1H-indole-3-carboxylate (**11a**)*

The isoxazolone (**9a**) (100 mg, 0.27 mmol) and triethylamine (0.2 mL) were refluxed in ethanol (10 mL) for 24 hours. The reaction mixture was left to cool to room temperature and resulting precipitate was collected to afford ethyl 2-(benzoxazol-2-ylamino)-1*H*-indole-3-carboxylate as white needles (36 mg, 41%), mp 178-180 °C. ^1H NMR ($CDCl_3$) δ 1.58 (t, *J* 6.9 Hz, 3H), 4.50 (q, *J* 6.9 Hz, 2H), 7.05 (t, *J* 7.3 Hz, 1H, Ar), 7.35 (t, *J* 8.3 Hz, 2H, Ar), 7.40 (t, *J* 7.9 Hz, 2H, Ar), 7.57 (d, *J* 8.0 Hz, 1H, Ar), 7.64-7.71 (m, 2H, Ar), 7.99 (bs, exchanged by D_2O addition, 1H, NH), 8.80 (bs, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 15.26, 60.67, 112.50, 118.58, 122.36, 124.34, 125.15, 127.95, 129.52, 140.51, 150.31, 155.52. FT-IR (KBr) ν_{max} /cm^{-1}: 3330, 2978, 1656, 1629, 1619, 1600, 1527, 1485, 1468, 1268, 1193, 740. Anal. Calc. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08%; Found: C, 67.10; H, 4.58; N, 13.31%.

*Ethyl 2-(benzoxazol-2-ylamino)-5-bromo-1H-indole-3-carboxylate (**11b**)*

The isoxazolone (**9b**) (100 mg, 0.22 mmol) and triethylamine (0.2 mL) were refluxed in ethanol (10 mL) for 24 hours. The reaction mixture was left to cool to room tempreture and resulting precipitate was collected to afford ethyl 2-(benzoxazol-2-ylamino)-5-bromo-1*H*-indole-3-carboxylate as white needles (40 mg, 44%), mp 156-158 °C. ^1H NMR ($CDCl_3$) δ 1.58 (t, *J* 6.9 Hz, 3H), 4.55 (q, *J* 6.9 Hz, 2H), 7.37 (t, *J* 7.6 Hz, 1H, Ar), 7.42 (t, *J* 7.7 Hz, 1H, Ar), 7.44 (d, *J* 8.7 Hz, 2H, Ar), 7.58 (bd, *J* 7.6 Hz, 3H, Ar), 7.99 (bs, exchanged by D_2O addition, 1H, NH), 8.80 (bs, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 15.25, 60.82, 112.60, 114.48, 116.88, 117.42, 120.01, 124.53, 125.24, 127.84, 132.37, 139.62, 150.30, 155.34. FT-IR (KBr) ν_{max}/cm^{-1}: 3323, 2979, 1658, 1618, 1599, 1571, 1485, 1274, 1193, 750. GC-MS (EI, 70 ev): *m/z* (%) 401 [(M^+ + 2), 59], 399 (M^+, 57), 257 (36), 274 (100), 246 (16), 218 (10), 102 (14), 90 (11), 76 (10), 29 (10).

*Ethyl 2-(benzoxazol-2-ylamino)-5-methyl-1H-indole-3-carboxylate (**11c**)*

The isoxazolone (**9c**) (100 mg, 0.22 mmol) and triethylamine (0.2 mL) were refluxed in ethanol (10 mL) for 24 hours. The reaction mixture was left to cool to room tempreture and resulting precipitate was collected to afford ethyl 2-(benzoxazol-2-ylamino)-5-methyl-1*H*-indole-3-carboxylate as white needles (42 mg, 48%), mp 166-168 °C. ^1H NMR ($CDCl_3$) δ 1.57 (t, *J* 7.0 Hz, 3H), 2.37 (s, 3H), 4.54 (q, *J* 7.0 Hz, 2H), 7.19 (d, *J* 8.1 Hz, 2H, Ar), 7.35 (t, *J* 7.8 Hz, 1H, Ar), 7.40 (t, *J* 7.8 Hz, 1H, Ar), 7.55 (s, 1H, Ar), 7.57 (d, *J* 8.0 Hz, 2H, Ar), 8.0 (bs, exchanged by D_2O addition, 1H, NH), 8.7 (bs, exchanged by D_2O addition, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 15.28, 21.12, 60.58, 112.46, 116.08, 118.86, 124.23, 125.12, 128.01, 130.01, 131.94, 137.93, 150.29, 155.63. FT-IR (KBr) ν_{max}/cm^{-1}: 3321, 2985, 1675, 1613, 1573, 1514, 1477, 1451, 1418, 1266, 1161, 1073, 738. Calc. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53%; Found: C, 67.91; H, 4.97; N, 12.32%.

*Ethyl 2-phenylaminoimidazo[2,1-b]benzothiazole-3-carboxylate (**12a**)*

This compound was prepared as lit.[14] procedure.

*Ethyl 2-(4-bromophenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate (**12b**)*

The isoxazolone (**10b**) (100 mg, 0.22 mmol) and triethylamine (0.2 mL) were refluxed in ethanol (10 mL) for 24 hours. The reaction mixture was left to cool to room tempreture and resulting precipitate was colleted to afford ethyl 2-(4-bromophenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate as white needles (51 mg, 57%), mp 179-181 °C. ^1H NMR ($CDCl_3$) δ 1.55 (t, *J* 7.2 Hz, 3H), 4.53 (q, *J* 7.2 Hz, 2H), 7.35 (t, *J* 7.8 Hz, 1H, Ar), 7.43 (d, *J* 8.7 Hz, 2H, Ar), 7.47 (t, *J* 7.8 Hz, 1H, Ar), 7.56 (d, *J* 8.7 Hz, 2H, Ar), 7.69 (d, *J* 7.8 Hz, 1H, Ar), 8.62 (bs, exchanged by D_2O addition, 1H, NH), 8.83 (bd, *J* 7.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 14.70, 60.63, 113.90, 116.82, 119.77, 123.58, 124.53, 126.45, 128.69, 130.32, 131.92, 134.38, 139.44, 151.80, 155.75, 160.32. FT-IR (KBr) ν_{max}/cm^{-1}: 3307, 2982, 1642, 1603, 1561, 1427, 1370, 1274, 1170, 1089, 756. GC-MS (EI, 70ev): *m/z* (%) 417 [(M^+ + 2), 45], 415 (M^+, 43), 371 (16), 369 (15), 290 (100), 263 (19), 262 (34), 161 (10), 134 (10), 102 (11). Anal. Calc. for $C_{18}H_{14}BrN_3O_2S$: C, 51.92; H, 3.36; N, 10.06%; Found: C, 51.78; H, 3.18; N, 10.14% and HRMS *m/z* 414.99900 ($C_{18}H_{14}BrN_3O_2S$ requires 414.99901).

*Ethyl 2-(4-methylphenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate (**12c**)*

The isoxazolone (**10c**) (100mg, 0.26 mmol) and triethylamine (0.2 mL) were refluxed in ethanol (10 mL) for 24 hours. The reaction mixture was left to cool to room temperature and resulting precipitate was colleted to afford ethyl 2-(4-methylphenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate as white needles (35 mg, 40%), mp 141-143 °C. ^{1}H NMR ($CDCl_3$) δ 1.55 (t, *J* 7.2 Hz, 3H), 2.34 (s, 3H), 4.58 (q, *J* 7.2 Hz, 2H), 7.17 (d, *J* 8.1 Hz, 2H, Ar), 7.34 (td, *J* 7.5 Hz, *J* 1.2 Hz, 1H, Ar), 7.46 (td, *J* 7.2 Hz, *J* 1.2 Hz, 1H, Ar), 7.53 (d, *J* 8.4 Hz, 2H, Ar), 7.69 (d, *J* 7.8 Hz, 1H, Ar), 8.47 (bs, exchanged by D_2O addition, 1H, NH), 8.87 (bd, *J* 7.8 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ 14.72, 20.762, 60.43, 117.01, 118.77, 120.44, 123.50, 124.30, 126.38, 128.92, 129.61, 131.55, 134.85, 137.71. 154.10, 162.30. FT-IR (KBr) ν_{max}/cm^{-1}: 3315, 2969, 1643, 1601, 1565, 1427, 1371, 1271, 1168, 1087, 757, 748.

*Ethyl 2-(4-nitrophenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate (**12d**)*

The isoxazolone (**10d**) (100 mg, 0.24 mmol) and triethylamine (0.2 mL) were refluxed in ethanol (10 mL) for 24 hours. The reaction mixture was left to cool to room tempreture and resulting precipitate was colled to afford ethyl 2-(4-nitrophenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate as yellow needles (48 mg, 53%), mp 221-223 °C (decomposed). ^{1}H NMR ($CDCl_3$) δ 1.59 (t, *J* 7.2 Hz, 3H), 4.58 (q, *J* 7.2 Hz, 2H), 7.41 (t, *J* 7.5 Hz, 1H, Ar), 7.51 (t, *J* 7.5 Hz, 1H, Ar), 7.75 (d, *J* 7.8 Hz, 1H, Ar), 7.81 (d, *J* 9.1 Hz, 2H, Ar), 8.24 (d, *J* 9.1 Hz, 2H, Ar), 8.84 (bd, *J* 8.4 Hz, 1H, Ar), 9.18 (bs, exchanged by D_2O addition, 1H, NH).^{13}C NMR ($CDCl_3$) δ 14.66, 61.11, 116.79, 123.77, 125.01, 125.58, 126.62, 127.79, 128.85, 130.67, 134.16, 146.23, 161.26. FT-IR (KBr) ν_{max}/cm^{-1}: 3286, 2979, 1648, 1600, 1573, 1322, 1281, 1110, 757. GC-MS (EI, 70ev): *m/z* (%) 382 (M$^+$, 88), 336 (11), 291 (24), 290 (100), 263 (16), 262 (43), 161 (19), 160 (14), 134 (14), 76 (10), 29 (16).

*Ethyl 2-(4-ethoxycarbonylphenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate(**12e**)*

The isoxazolone (**10e**) (100 mg, 0.25 mmol) and triethylamine (0.2 mL) were refluxed in ethanol (10 mL) for 24 hours. The reaction mixture was left to cool to room tempreture and resulting precipitate was colleted to afford ethyl 2-(4-ethoxycarbonylphenyl)aminoimidazo[2,1-b]benzothiazole-3-carboxylate as white needles (54 mg, 60%), mp 191-193 °C. ^{1}H NMR ($CDCl_3$) δ 1.41 (t, *J* 7.2 Hz, 3H), 1.56 (t, *J* 7.2 Hz, 3H), 4.43 (q, *J* 7.2 Hz, 2H), 4.53 (q, *J* 7.2 Hz, 2H), 7.35 (t, *J* 7.2 Hz, 1H, Ar), 7.47 (t, *J* 7.2 Hz, 1H, Ar), 7.70 (d, *J* 7.8 Hz, 3H, Ar), 8.02 (d, *J* 7.8 Hz, 2H, Ar), 8.83 (bd, *J* 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 14.41, 14.65, 60.54, 60.78, 116.84, 123.01, 123.60, 124.65, 126.45, 128.77, 131.03, 134.30, 144.45, 147.01, 151.86, 160.23, 166.48. FT-IR (KBr) ν_{max}/cm^{-1}: 3393, 2978, 1716, 1691, 1601, 1563, 1461, 1421, 1375, 1174, 1085, 754.

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References

1. Ulrich, H.; Tilley, J. N.; Sayigh, A. A.; *J. Org. Chem*. **1962**, *27*, 2160.
2. Desarlo, F.; Renzi, G.; *Tetrahedron* **1966**, *22*, 2995.
3. Woodman, D. J.; Stonebraker, P. M.; Weiler, L.; *J. Am. Chem. Soc*. **1976**, *98*, 6036.
4. Woodman, D. J.; Campbell, W. H.; Derose, E. F.; *Heterocycles* **1977**, *7*, 247.
5. Bossio, R.; Marcaccini, S.; Pepino, R.; Paoli, P.; *J. Heterocyclic. Chem*. **1993**, *30*, 33.
6. Donati, C.; Janowski, W. K.; Prager, R. H.; Taylor, M. R.; Vilkins, L. M.; *Aust. J. Chem*. **1989**, *42*, 2161.
7. Prager, R. H.; Rosenzweig, T. K.; Singh, Y.*; Aust. J. Chem*. **1992**, *45,* 1825.
8. Prager, R. H.; Razzino, P.; *Aust. J. Chem*. **1994***, 47,* 1673.
9. Baradarani, M. M.; Clark, A.; Prager, R. H.; *Aust. J. Chem*. **1998**, *51*, 491.
10. Doleschall, G.; *Tetrahedron Lett.* **1988**, *29,* 6339.
11. Khalafy, J.; Prager, R. H.; *J. Sci. I. R. Iran* **2000**, *11*, 32.
12. Khalafy, J.; Molla Ebrahimlo, A. R.; Eisavi, R.; Akbari Dilmaghani, K.; *Arkivoc* **2005**, *xiv,* 59.
13. Khalafy, J.; Prager, R. H.; Smith, J. A.; *J. Chem. Res(M).* **1999**, 518.
14. Khalafy, J.; Molla Ebrahimlo, A. R.; Akbari Dilmaghani, K.*; J. Chin. Chem. Soc*. **2004**, *51*, 1347.
15. Worrall, D. E.; *J. Am. Chem. Soc*. **1923**, *45*, 3092.
16. Zvilichovsky, G.; Gurvich, V.; Segev, S.; *J. Org. Chem*. **1995**, *60*, 5250.
17. Tuteja, N.; Pham, T.; Tuteja, R.; Ocham, A.; Falaschi, A.; *Biochem. Biophys. Res. Commun*. **1997**, *236*, 636.
18. Stiborova, M.; Bieler, C. A.; Wiessler, M.; Frei, E.; *Biochem. Pharmacol*. **2001**, *62*, 1675.
19. Perrin, D. D.; Armarego, W. L. F.; *Purification of Laboratory Chemicals,* Pergamon Press: Oxford, U.K., 1988.
20. Jeffery, D.; Prager, R. H.; Turner, D.; Dreimanis, M.; *Tetrahedron* **2002**, *58*, 9965.

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