Tetrahedron Letters 51 (2010) 575–578

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# A general approach to indole-7-yl derivatives of isoxazole, oxadiazole, thiadiazole and pyrazole

Alexandre M. Polozov, Georgeta Hategan, Hua Cao, Alex S. Kiselyov, Wayne Zeller, Jasbir Singh *

*deCODE Chemistry, Inc, 2501 Davey Road, Woodridge, IL, USA*

ARTICLE INFO

*Article history:*
Received 19 September 2009
Revised 9 November 2009
Accepted 16 November 2009
Available online 20 November 2009

ABSTRACT

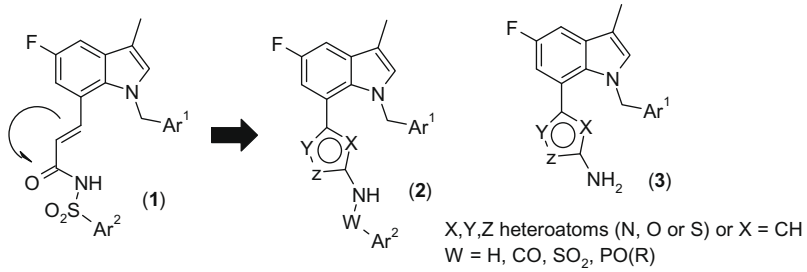
Isosteric replacement of the α,β-unsaturated amide at the C-7 position of indoles with a diverse set of five-membered amino-heterocycles including isoxazole, oxadiazole, thiadiazole and pyrazole followed by subsequent derivatization of the heterocyclic amino group to yield amides, sulfonamides and phosphoramides is described. Distinctive features of these procedures include the versatility and robust nature of the synthetic steps along with the high yields of the targeted molecules.



Recently, we have reported antagonists of the human $EP_3$ receptor as novel platelet aggregation inhibitors that do not extend the bleeding time[1] and thus are of great interest as potential antithrombotic agents. These potent, isoform selective $hEP_3$ antagonists, based on the 1,7-indole disubstituted series **1** (Scheme 1), showed an excellent activity in platelet aggregation assays.[1,2] These analogues contain the acylsulfonamide functionality as a key pharmacophoric feature. Based on both extensive SAR[3] data and our modelling studies[4] we sought to explore heterocyclic isosteres for the –C═CH–CO– fragment in **1**. This modification was expected to affect the topology, steric and electronic features of the sulfonamide bearing appendage, as shown by the general structure **2**.[5] In particular, we were interested in preparing 1-alkylaryl 7-heterocyclic indole derivatives **2** as a diverse set of $EP_3$ receptor antagonist chemotypes. However, examination of the literature revealed lack of a general approach to indoles featuring five-membered amino-heterocycles at C-7 position.[6] In this report, we describe a versatile and flexible approach to a diverse set of five-membered amino-heterocycles **3** from the 1,7-disubstituted indole derivatives **4** (Scheme 2). A subsequent derivatization of the amino group in **3** is expected to furnish the targeted substituted indoles **2**.

Formation of 7-carbomethoxy indole from 7-bromoindole by metalation with *n*-BuLi, followed by reaction with methyl chloroformate has been reported earlier.[7] *N*-Alkylation of indole **6**[8] provided 7-bromo indole **7** (Scheme 3). Treatment of 7 with *n*-BuLi (1.5 equiv) followed by the addition of ethyl chloroformate (2.0 equiv) afforded the desired ester derivatives **4** (Table 1) in good to excellent isolated yields (76–90%) and purity.[9] These key intermediates were subsequently converted into a diverse set of heterocycles as described below (Scheme 4).

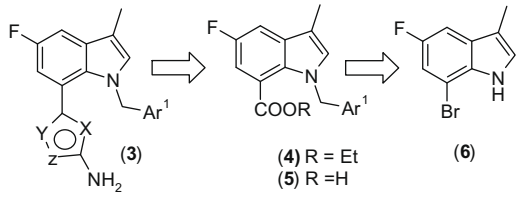
Reaction of **4** with hydrazine provided the corresponding hydrazides **8** in 70–90% yield. Subsequent exposure of **8** to cyanogen bromide in aqueous *p*-dioxane in the presence of sodium or potassium bicarbonate furnished 2-amino-1,3,4-oxadiazoles **9**




**Scheme 1.** Heterocycles as isosteres for α,β-unsaturated amides.

* Corresponding author. Tel.: +1 630 904 2218.
*E-mail address:* jsingh@decode.com (J. Singh).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.11.073



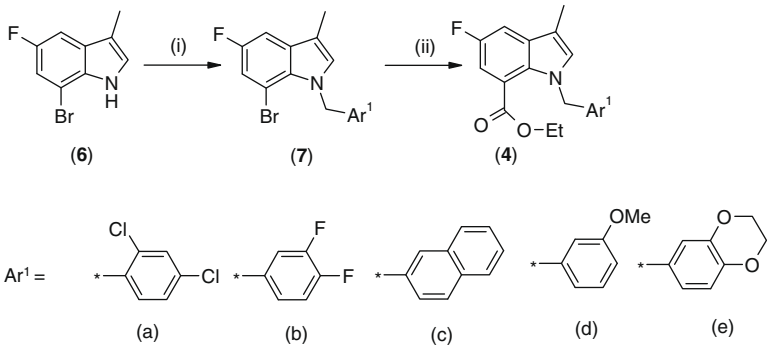

**Scheme 2.** Retrosynthetic analysis.

(53–90% overall yields). Similar to a reported procedure,[10] the hydrolysis of **4** followed by the reaction of resultant acid **5** with thiosemicarbazide in the presence of $POCl_3$, provided 2-amino-1,3,4-thiadiazoles **10**.

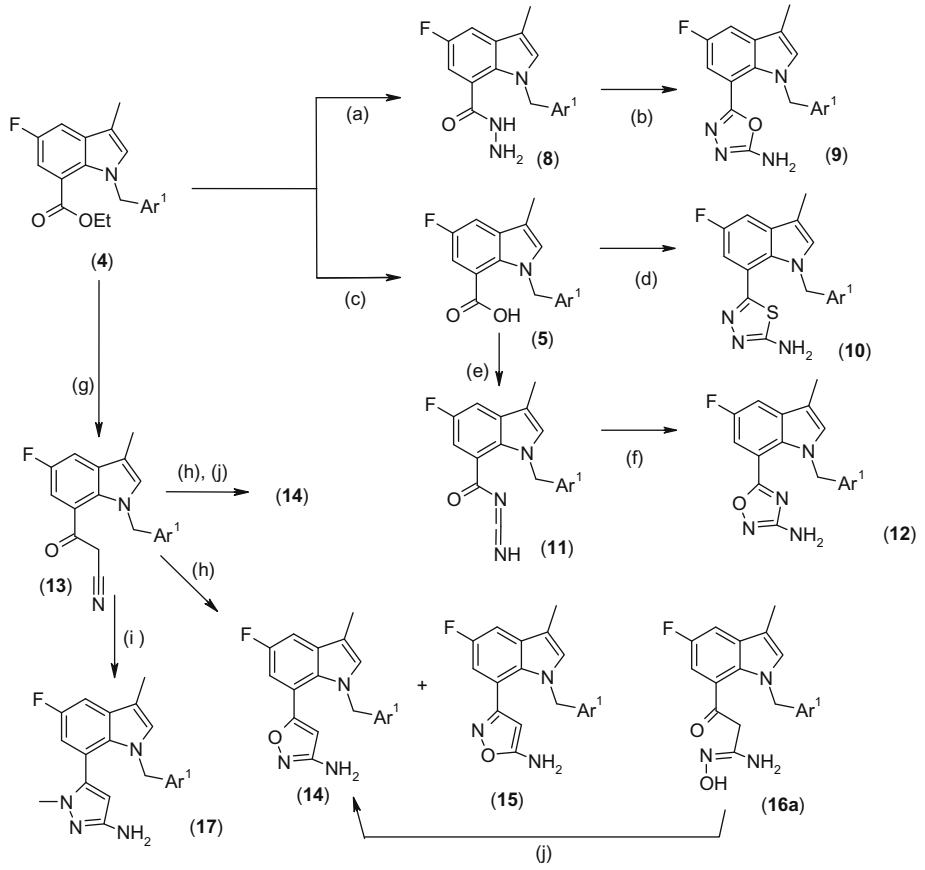
**Table 1**
Yields of 7-substituted indoles from (**6**)

| | | | | |
|---|---|---|---|---|
| **7a** | **7b** | **7c** | **7d** | **7e** |
| 64% | 95% | 90% | 93% | 80% |
| **4a** | **4b** | **4c** | **4d** | **4e** |
| 90% | 85% | 90% | 83% | 76% |

The carboxylic acid **5a** was converted to the acid chloride which was immediately converted to the 7-carboxylic acid iminomethyleneamide, **11a** (Scheme 4).[11,12] This key intermediate was subse-




**Scheme 3.** Synthesis of C7-indole esters (**4**). Reagents and conditions: (i) (a) NaH, DMF, −10 °C, (b) $Ar_1$-$CH_2$-Br; (ii) (a) *n*-BuLi, $Et_2O$, (b) EtOCOCl, −78 °C–rt, 1 h.




**Scheme 4.** Reagents and conditions: (a) $NH_2NH_2$, MTBE, 120 °C, 12 h; (b) BrCN/$NaHCO_3$, *p*-dioxane-water, rt, 2 h; (c) 2 N NaOH, MeOH/THF (1:1), 75 °C, 1 h; (d) $NH_2C(S)NH_2NH_2$, $POCl_3$, 120 °C, 30 min; (e) (i) $(COCl)_2$/DMF cat, THF, rt, 5 min; (ii) cyanoamide, 2 N NaOH, THF–$H_2O$, rt, 5 min; (f) $NH_2OH$, pyridine, 60 °C, 4 h; (g) *n*BuLi, $CH_3CN$, THF, −78 °C→rt, 1 h; (h) $NH_2OH$·HCl or $(NH_2OH)_2SO_4$, NaOH, $H_2O$–EtOH, (2:3, v/v), reflux, 17 h; (j) 36% aq HCl, 90 °C, 2 h; (k) (l) $NH_2NHCH_3$, HOAc, *i*PrOH, heat.

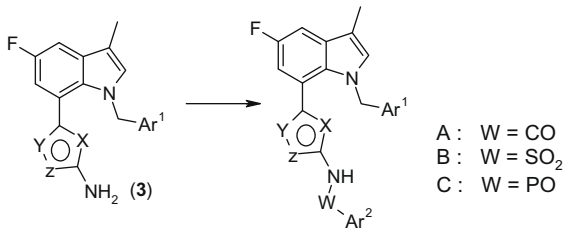
**Table 2**
Yields for individual intermediates corresponding to the steps described in Scheme 4

| Amine heterocycle | For $Ar^1$ substituents, see legend in Scheme 3 | | | | |
|---|---|---|---|---|---|
| | a | b | c | d | e |
| 5 | 95 | | | 94 | 94 |
| 8 | 75 | | | 86 | 79 |
| 9 | 79 | | | 53 | 62 |
| 10 | 47 | 52 | | | |
| 11 | 68 | | | | |
| 12 | 44 | | | | |
| 13 | 93 | 75 | 80 | | |
| 14 | 39 | 29* 49** | 37 | | |
| 15 | 11 | 17 | | | |
| 17 | | 30 | | | |

* From chromatographic separation.
** Following acid hydrolysis step prior to purification.

quently reacted with two equivalents of hydroxylamine in pyridine to yield the 1,2,4-oxadiazole **12a**.

A number of methods for the preparation of amino-5-aryl isoxazoles starting from alkyl propiolates, β-ketonitriles or amidoxime have been reported.[13,14] Due to the accessibility and versatility of β-ketonitriles **13** we used these in our synthetic sequence. Cyclization of β-ketonitriles with hydroxylamine is known to be non-regioselective, leading to the formation of a mixture of 3-amino- and 5-amino-isoxazoles.[15] β-Ketonitriles **13** were readily accessible in 75–80% yields by reacting the respective carbanion of acetonitrile with esters **4**. Subsequent reaction of **13** with hydroxylamine led to the regioisomeric isoxazole derivatives **14** and **15**. Alternatively, reaction of β-ketonitrile **13** with hydroxylamine under basic conditions followed by hydrolytic ring opening of the acid labile 5-amino-isoxazole isomer with concentrated HCl provided 3-amino-isoxazoles **14a–c**.[16] Reaction of β-ketonitrile **13a** with hydroxylamine under basic conditions (EtOH/$H_2O$, 1:1, v/v, 80 °C, 10 h), provided **14a** and **15a** as major products along with a small amount (~10%) of the amidoxime intermediate **16a**. Upon treatment with aqueous HCl in EtOH/$H_2O$, **16a** cyclized to result in **14a** in ~75% isolated yield. Similarly, **13b** and **13c** were converted to **14b** and **14c**, respectively, except the initial products following reaction with hydroxyl amine were treated with aq HCl before isolation of the final products, **14b** and **14c** in yields reported in Table 2. The structure of 3-amino-isoxazole **14a** was unequivocally confirmed by a single crystal X-ray analysis.[5] Alternatively, the reaction of β-ketonitrile **13b** with methyl hydrazine afforded 3-amino pyrazole **17b** in 30% yield. Yields for the representative heterocyclic intermediates featured on Scheme 4 are summarized in Table 2.




**Scheme 5.** Derivatization of the amino-heterocycle.

A diverse set of amino heterocyclic intermediates (**9**, **10**, **12**, **14**, **15** and **17**) were subsequently reacted with a variety of aryl and heteroaryl acyl chlorides, sulfonyl chlorides and phosphoryl chlorides to provide the corresponding amide, sulfonamide and phosphoramide derivatives, respectively, (Scheme 5). Generally, the amides and phosphoramides were obtained in good to excellent

**Table 3**
Heterocyclic amides (A), sulfonamides (B) and phosphoramides (C)

| Compound | X | Y | Z | W | $Ar^1$ | $Ar^2$ | Yield (%) |
|---|---|---|---|---|---|---|---|
| **18** | O | N | N | CO | 2,4-Dichloro phenyl | $CF_3$ | 90 |
| **19** | O | N | N | CO | 2,4-Dichloro phenyl | 4-Fluoro phenyl | 55 |
| **20** | O | N | N | CO | 2,4-Dichloro phenyl | Isoxazol-5yl | 34 |
| **21** | O | N | N | CO | 2,4-Dichloro phenyl | 3,5-Dichloro phenyl | 37 |
| **22** | O | N | N | CO | 2,4-Dichloro phenyl | 3,4-Difluoro phenyl | 57 |
| **23** | O | N | N | CO | 2,4-Dichloro phenyl | 2,4-Difluoro phenyl | 41 |
| **24** | O | N | N | CO | 2,4-Dichloro phenyl | 2,4-Dichloro phenyl | 74 |
| **25** | O | N | N | CO | 2,4-Dichloro phenyl | 5-[2,2-Difluoro-benzo[1,3]dioxole] | 35 |
| **26** | O | N | N | CO | 2,4-Dichloro phenyl | 2-Furanyl | 55 |
| **27** | O | N | N | $SO_2$ | 2,4-Dichloro phenyl | $CH_3$ | 26 |
| **28** | O | N | N | $SO_2$ | 2,4-Dichloro phenyl | 2,4,5-Trifluoro phenyl | 17 |
| **29** | O | N | N | $SO_2$ | 2,4-Dichloro phenyl | 4,5-Dichloro thiophenyl | 27 |
| **30** | O | N | N | $SO_2$ | 2,4-Dichloro phenyl | 3,4-Dichloro phenyl | 17 |
| **31** | O | N | N | $SO_2$ | 2,4-Dichloro phenyl | 3,4-Difluoro phenyl | 18 |
| **32** | O | N | N | PO | 2,4-Dichloro phenyl | Phenyl | 49 |
| **33** | O | N | N | PO | 2,4-Dichloro phenyl | 2,4-Dichloro phenoxy | 25 |
| **34** | N | O | N | $SO_2$ | 2,4-Dichloro phenyl | 4,5-Dichloro thiophenyl | 10 |
| **35** | CH | O | N | $SO_2$ | 3,4-Difluoro phenyl | 4,5-Dichloro thiophenyl | 18 |
| **36** | CH | O | N | $SO_2$ | 3-Methoxy phenyl | 3,4-Difluoro phenyl | 22 |
| **37** | CH | O | N | $SO_2$ | 2,3-Dihydro-benzo[1,4]dioxan-6-yl | 3,4-Difluoro phenyl | 10 |
| **38** | CH | O | N | $SO_2$ | 2,4-Dichloro phenyl | 2,4.5-Trifluoro phenyl | 27 |
| **39** | CH | O | N | $SO_2$ | 2,4-Dichloro phenyl | 4,5-Dichloro thiophenyl | 35 |
| **40** | CH | O | N | $SO_2$ | 2,4-Dichloro phenyl | 3,4-Dichloro phenyl | 43 |
| **41** | CH | O | N | $SO_2$ | 2,4-Dichloro phenyl | 3,4-Difluoro phenyl | 46 |
| **42** | CH | O | N | $SO_2$ | 3,4-Difluoro phenyl | 2,4.5-Trifluoro phenyl | 16 |
| **43** | CH | O | N | $SO_2$ | 3,4-Difluoro phenyl | 2,4,5-Trifluoro phenyl | 16 |
| **44** | CH | O | N | $SO_2$ | 3,4-Difluoro phenyl | 3,4-Difluoro phenyl | 44 |
| **45** | CH | O | N | $SO_2$ | 2-Naphthyl | 2,4,5-Trifluoro phenyl | 19 |
| **46** | CH | O | N | $SO_2$ | 2-Naphthyl | 4,5-Dichloro thiophenyl | 33 |
| **47** | CH | O | N | $SO_2$ | 2-Naphthyl | 3,4-Dchloro phenyl | 33 |
| **48** | CH | O | N | $SO_2$ | 2-Naphthyl | 3,4-Difluoro phenyl | 24 |
| **49** | CH | N | O | $SO_2$ | 3,4-Difluoro phenyl | $CH_3$ | 36 |
| **50** | CH | N-Me | N | $SO_2$ | 3,4-Difluoro phenyl | $CH_3$ | 89 |
| **51** | CH | N-Me | N | $SO_2$ | 3,4-Difluoro phenyl | 4,5-Dichloro thienyl | 33 |

The unoptimized yields shown are from the corresponding amine.

yields (50–90%), while reactions with substituted phenyl and heterocyclic sulfonyl chlorides provided poor to modest yield of the targeted acyl sulfonamides (typically 10–50%).

The flexibility and general versatility of the synthetic procedures described above are further demonstrated by the preparation of a diversity of 7-substituted indoles (Table 3).

In summary, versatile, robust and generally high-yielding reaction sequences have been described for the elaboration of 7-carboxylate /carboxylic acid substituents of indoles to provide a diverse set of five-membered amino-heterocycles.[17] The resulting amines were further derivatized to furnish the respective amide, sulfonamide and phosphoramide derivatives **18–51**. Several derivatives showed 1–5 μM activity in the functional rat platelet aggregation assay prompting further evaluation of these lead candidates. Details of their biological evaluation will be reported elsewhere.[5]

## References and notes


1. Singh, J.; Zeller, W.; Zhou, N.; Hategen, G.; Mishra, R.; Polozov, A.; Yu, P.; Onua, E.; Zhang, J.; Zembower, D.; Kiselyov, A.; Ramírez, J.; Sigthorsson, G.; Bjornsson, J.; Thorsteinsdottir, M.; Andrésson, Þ.; Bjarnadottir, M.; Magnusson, O.; Fabre, J.; Stefansson, K.; Gurney, M. A. C. S. *Chem. Biol.* **2009**, *4*, 115–126.
2. Singh, J.; Zhou, N.; Hategan, G.; Zeller, W.; Polozov, A.; Goldsmith, M.; Krohn, M.; Anderson, H.; Mishra, R.; Zhang, J.; Onua, E.; Ramirez, J.; Palsdottir, G.; Halldorsdottir, G.; Andresson, T.; Gurney, M. 230th ACS National Meeting, Washington, DC, Aug 28–Sept 1, 2005. MEDI (Abstract #250).
3. Singh, J.; Zeller, W.; Zhou, N.; Hategen, G.; Mishra, R.; Polozov, A.; Yu, P.; Onua, E.; Zhang, J.; Ramírez, J.; Sigthorsson, G.; Thorsteinnsdottir, M.; Kiselyov, A.; Zembower, D.; Andrésson, Þ.; Gurney, M., *J. Med. Chem.* **2009**, Accepted.
4. We have generated a six-point pharmacophore for the EP3 receptor. Strategies utilized in the development of this pharmacophore will be reported in a forthcoming disclosure, being submitted to *J. Chem. Int. Model.*
5. Hategan, G.; Polozov, A. M.; Zeller, W.; Cao, H.; Mishra, R. M.; Kiselyov, A. K.; Ramirez, J.; Halldorsdottir, G.; Andrésson, Þ.; Gurney, M. E.; Singh, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6797–6800.
6. (a) Black, D.; Bowyer, M.; Kumar, N. *Tetrahedron* **1977**, *53*, 8573–8584. This report utilizes highly electron rich indole and Vilsmeier reaction methodology using the pyrrolidin-2-one approach for synthesis indol-7-yl-pyrrole; (b) A relevant paper describes synthesis of a trisubstituted indole-7-triazolyl derivatives: Contour-Galcera, M.; Alban, S.; Pascale, P.; Pierre, R. *Bioorg. Med.* **2009**, *19*, 6797–6800. *Chem. Lett.* **2005**, *15* 3555–3559.; For recent patent examples see: (c) US20030069245, describes preparartion of several aminosubstituted 5-membered heteroaromatics.; (d) WO2009071577, aminooxadiazole derivatives.
7. Li, L.; Martins, A. *Tetrahedron Lett.* **2003**, *44*, 689–692.
8. Zegar, S.; Tokar, C.; Enache, L.; Rajagopol, V.; Zeller, W.; O'Connell, M.; Singh, J.; Muellner, F.; Zembower, D. E. *Org. Process Res. Dev.* **2007**, *11*, 747–753.
9. Smaller excesses (1.1–1.2 equiv) of *n*-BuLi in $Et_2O$ or THF followed by addition of 1.2 equiv of methyl chloroformate afforded both poor yield and low purity of the desired acylation products; LCMS analysis of crude reaction mixtures indicated a considerable amount of unreacted bromo derivative **6** was present.
10. (a) Pomslb, K. T.; Huseby, R. M. *J. Org. Chem.* **1966**, *31*, 3528–3531; (b) Turner, S. M.; Myers, B.; Gadie, A. J.; Nelson, R.; Pape, J. F.; Saville, J. C.; Doxey, T. L.; Berridge *J. Med. Chem.* **1988**, *31*, 902–906; (c) Tsuji, T.; Takenaka, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 637–638; (d) Foroumadi, A.; Tabatabai, S. A.; Gitinezhad, G.; Zarrindast, M. R.; Shafiee, A. *Pharm. Pharmacol. Commun.* **2000**, *6*, 31–34; (e) Foroumadi, A.; Soltani, F.; Moshafi, M. H.; Ashraf-Askari, R. *Farmaco* **2003**, *58*, 1023–1028; (f) Carvalho, S. A.; daSilva, E. F.; Santa-Rita, R. M.; de Castro, S. L.; Fraga, C. A. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5967–5970.
11. Howard, J. C.; Youngblood, F. E. *J. Org. Chem.* **1966**, *31*, 959–961.
12. Acid **5** was reacted with oxalyl chloride to yield the respective acyl chloride. Sodium hydrogen cyanamide (prepared from cyanamide and 2 N NaOH) was reacted with **5** in THF for 2 h at rt, the reaction mixture was partitioned between EtOAc and 10% aq HCl (4:1), the organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to furnish the cyanamide **11a** in a 68% overall yield.
13. (a) Iwai, I.; Nakamura, N. *Chem. Pharm. Bull.* **1966**, *14*, 1277–1286; (b) Kloetzer, W.; Bretschneider, H.; Fitz, E.; Reiner, R.; Bader, G. *Monatsh. Chem.* **1970**, *101*, 1109–1122; (c) Stachel, H. D. *Chem. Ber.* **1963**, *96*, 1088–1097; (d) Uno, H.; Kurokawa, M.; Nishimura, H. *Chem. Pharm. Bull.* **1976**, *24*, 644–647.
14. (a) Rouchaud, J.; Gustin, F.; Moulard, C. *Bull. Soc. Chim. Belg.* **1991**, *102*, 545–555; (b) Takasa, A.; Murabayashi, A.; Sumimoto, S.; Ueda, S.; Makisumi, Y. *Heterocycles* **1991**, *32*, 1153–1158.
15. Claisse, J. A.; Foxton, M. W.; Gregory, G. I.; Sheppard, A. H.; Tiley, E. P.; Warburton, W. K.; Wilson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2241–2249.
16. A reaction sequence for the regioselective synthesis of 5-amino-isoxazole derivative of 3-(cyanoacetyl indole) using buffered media has been reported: Slatt, J.; Janosik, T.; Wahlsrom, K.; Bergman, J. *J. Heterocycl. Chem.* **2005**, *42*, 141–143.
17. The synthesis of **14a** and its transformation to **39** is provided below as a representative example.

*7-Bromo-1-(2,4-dichlorobenzyl)-5-fluoro-3-methyl-1H-indole* (**7a**). NaH (60% in oil, 526 mg, 13.15 mmol) was added to a solution of **6** (2 g, 8.77 mmol) in DMF (30 mL) at −10 °C. Reaction mixture was warmed to rt and then stirred for 30 min. A solution of 2,4-dichlorobenzyl chloride (2.06 g, 10.52 mmol) in DMF (10 mL) was added at −10 °C. The reaction mixture was allowed to warm to rt, stirred for 30 min and then the reaction was quenched with 10% HCl/water/ether (1:1:2, 40 mL). The aqueous layer was extracted with ether (2 × 10 mL) and the combined organic layers were washed with water (3 × 75 mL), brine (75 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford crude product as a brown solid. Ether (4 mL) was added and the solution was cooled, and the off-white solid was filtered to afford indole **7a** (2.49 g, 73%). $R_f$ = 0.70 (EtOAc/hexanes, 1:5). MS ($ESI^+$) *m*/*z*: 388 ($M^+$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 5.69 (s, 2H), 6.22 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.89 (d, *J* = 0.5 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.13 (ddd, *J* = 8.4, 2.0, 0.4 Hz, 1H), 7.19 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.41 (d, *J* = 2.0 Hz, 1H).

*5-[1-(2,4-Dichloro-benzyl)-5-fluoro-3-methyl-1H-indol-7-yl]-isoxazol-3-ylamine* (**14a**). *n*-BuLi (1.6 M in hexanes, 0.97 mL, 1.55 mmol) was added under an Argon atmosphere to a solution of **7a** (400 mg, 1.03 mmol) in ether (7 mL) at −78 °C over 7 min. The reaction mixture was stirred at −78 °C for 30 min. Ethyl chloroformate (0.2 mL, 2.07 mmol) was added slowly and the reaction mixture was warmed up to rt, stirred at rt for 30 min and then the reaction was quenched with 10% aqueous HCl (5 mL). The organic layer was washed with water (2 × 10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford ester **4a** (386 mg, 98%) as a brown oil. $R_f$ = 0.45 (EtOAc/hexanes, 1:19). MS ($APCI^+$): *m*/*z* 379 (M+). This material was used without further purification.

Acetonitrile (1.01 mL, 19.25 mmol) was slowly added over 3 min to a solution of *n*-BuLi (2.5 M, 8.7 mL, 21.66 mmol) in THF (90 mL) at −78 °C. The reaction mixture was stirred for additional 15 min at −78 °C and a solution of the ester **4a** (3.66 g, 9.63 mmol) in THF (20 mL) was added slowly and the reaction mixture was allowed to warm to rt over 30 min. The reaction mixture was cooled to −78 °C and 10% aqueous HCl (40 mL) was added followed by ether (40 mL). The aqueous phase was extracted with ether (2 × 40 mL). The combined organic extracts were washed with water (3 × 100 mL), brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield crude product (3.61 g, 100%) as a brown oil. The crude oil, upon trituration with hexane (3 × 4 mL) afforded the β-ketonitrile **13a** 2.70 g (75%) as a light brown solid. $R_f$ = 0.11 (hexanes/acetone, 9:1). This material was used without any further purification. $^1H$ NMR (400 MHz, $CDCl_3$), 2.32 (s, 3H), 3.66 (s, 2H), 5.42 (s, 2H), 6.08 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 1.6 Hz, 1H), 7.09–7.12 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.26 (s, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.51–7.54 (dd, *J* = 8.8, 2.8 Hz, 1H). To a mixture of β-ketonitrile **13a** (2.33 g, 6.2 mmol, 1 equiv) in water–ethanol (2:3, 22 mL) was added sodium hydroxide (295 mg, 7.15 mmol) and hydroxylamine sulfate (0.506 g, 3.42 mmol) and the reaction mixture was heated to reflux for 20 h. A solution of 36% aqueous HCl (0.8 mL) was added and the reaction mixture was heated to reflux for additional 2 h. The reaction mixture was cooled to 0 °C and the reaction was quenched through the addition of saturated aqueous $NaHCO_3$ (25 mL), followed by solid $Na_2CO_3$ (2.5 g). Mixture was extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with water (2 × 50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield crude product as brown oil. Purification by flash silica gel chromatography, using $CH_2Cl_2$ as eluent, afforded 1.04 g (43%) of the compound **14a** as brown crystals. $R_f$ = 0.25 ($CH_2Cl_2$). $^1H$ NMR (400 MHz, CDCl3) δ 2.31 (s, 3H), 3.89 (br s, 2H), 5.14 (s, 2H), 5.61 (s, 1H), 6.21 (d, *J* = 8 Hz, 1H), 6.88 (s, 1H), 6.92–6.95 (dd, *J* = 9.2, 2.4 Hz, 1H), 7–7.02 (dd, *J* = 8, 2 Hz, 1H), 7.33 (s, 1H), 7.35–7.37 (dd, *J* = 9.2, 2.4 Hz, 1H). MS ($ESI^-$) *m*/*z*: 392 (M+1). LCMS 97%.

*4,5-Dichloro-thiophene-2-sulfonic acid {5-[1-(2,4-dichloro-benzyl)-5-fluoro-3-methyl-1H-indol-7-yl]-isoxazol-3-yl}-amide* (**39**). To a suspension of **14a** (180 mg, 0.447 mmol) in 0.5 ml pyridine was added DMAP (81 mg, 0.67 mmol, 1.5 equiv). This mixture was briefly heated in a 70 °C bath until a clear solution was obtained. Then, 2,3-dichlorothiophene-5-sulfonyl chloride (140 mg, 0.536 mmol, 1.2 equiv) was added to the solution at rt and stirred for 3 h. The mixture was concentrated in vacuo to give an oil and then dissolved in EtOAc (15 mL). The organic layer was washed with 10% aqueous HCl (2 × 3 mL), water (2 × 3 mL), brine (2 × 3 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide 280 mg of a residue. Purification of this residue by column chromatography using 20–50% EtOAc/ hexanes gave 100 mg (35%) of the pure desired product as white solid. $^1H$ NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 5.05 (s, 2H), 6.24 (d, *J* = 8.0 Hz, 1H), 6.34 (s, 1H), 6.90 (s, 1H), 6.97 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.03 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.3 (d, *J* = 2.0 Hz, 1H), 7.41 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.45 (s,1H), 7.55 (br s, 1H). MS($ESI^-$) *m*/*z*: 604 (M−1). HPLC (Phenomenex Prodigy $C_{18}$ column, 4.6 × 150 mm, 5 μm, 254 nm) eluted using a gradient elution 95/5 to 5/95 A/B over 20 min at a flow rate of 1.0 mL/min methanol) = 99.4%.