Pyrrolotriazine-5-carboxylate ester inhibitors of EGFR and HER2 protein tyrosine kinases and a novel one-pot synthesis of C-4 subsitituted pyrrole-2,3-dicarboxylate diesters[1]

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Abstract: Pyrrolotriazines with an ester group at C-5 were prepared and evaluated as inhibitors of the EGFR and HER2 receptor tyrosine kinases, validated targets for cancer therapy. The C-5 ester (**15**) was at least as potent as its C-6 ester analogue (**17**), an example of a known series of pyrrolotriazine EGRF/HER2 kinase inhibitors that show good biochemical and cellular activity. The C-5 esters were synthesized from pyrrole 2,3-diesters that were made by a new, one-pot procedure. This involved reaction of readily available *N*-tosyl derivatives of α-amino acid esters or ketones with triphenylphosphine and diethyl acetylenedicarboxylate to form 3-pyrrolines via an intramolecular Wittig olefination. The 3-pyrroline intermediates were not isolated but treated directly with base to eliminate toluenesulfinic acid and generate the pyrrole 2,3-diesters in good yield.

Key words: pyrrolotriazine, EGFR, HER2, pyrrole, intramolecular Wittig reaction.

Résumé : On a préparé des pyrrolotriazines portant un groupe ester en position C-5 et on les a évalués comme inhibiteurs des kinases EGFR et HER2 du récepteur de tyrosine qui sont des cibles validées pour la thérapie du cancer. L'ester en C-5 (**15**) est au moins aussi puissant que son analogue **17**, l'ester en C-6, comme exemple d'une série connue de pyrrolotriazines qui peuvent agir comme inhibiteurs de la kinase EGRF/HER2 et qui présentent une bonne activité biochimique et cellulaire. Les esters en C-5 ont été synthétisés à partir de 2,3-diesters du pyrrole qui avaient été préparés par une nouvelle méthode monotope. Celle-ci implique la réaction des dérivés *N*-tosylés d'esters d'acides α-aminés ou de cétones avec de la triphénylphosphine et de l'acétylènedicarboxylate de diéthyle qui conduit à la formation de 3-pyrrolines par le biais d'une oléfination de Wittig intramoléculaire. Les intermédiaires 3-pyrrolines n'ont pas été isolés, mais traités directement avec une base pour éliminer l'acide toluènesulfinique et générer les 2,3-diesters du pyrrole avec de bons rendements.

Mots clés : pyrrolotriazine, EGFR, HER2, pyrrole, réaction de Wittig intramoléculaire.

[Traduit par la Rédaction]

Introduction

Receptor tyrosine kinases catalyze the phosphorylation of proteins that are involved in the signaling processes that control cell proliferation and differentiation. Since aberrant activation of this kinases results in uncontrolled cell growth, extensive drug discovery efforts have been made to find selective, small molecule inhibitors for the treatment of cancers (1). The epidermal growth factor receptor (EGFR) and HER2 are members of the ErbB family of receptor tyrosine kinases and they have been clinically validated as targets for cancer therapy (2). Their frequent coexpression in a variety of tumor types and their capacity to form heterodimers with other members of the ErbB family provides a strong rationale for simultaneous targeting of both receptors. The pyrrolo[2,1-*f*][1,2,4]triazine nucleus has been identified as a novel scaffold for ATP-competitive kinase inhibitors (3). BMS scientists have shown that pyrrolotriazine analogs (**1**) that carry an ester group at C-6 and a relatively large lipohilic amino group at C-4 can show potent inhibition of both the EGFR and the HER2 kinases (4). The C-6 ester group can be modified to further improve biochemical po-

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Dedicated to Professor Walter A. Szarek for his scientific contributions, and just as important, for his long-time friendship.

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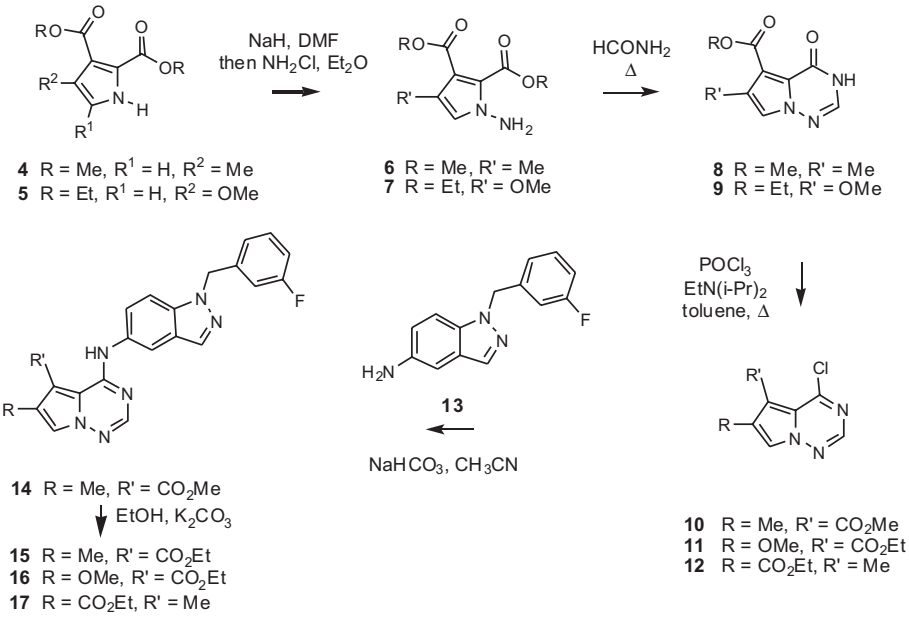
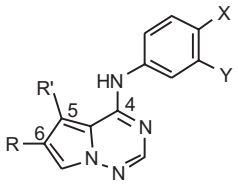
Scheme 1.



tency and cellular activity. To explore the structure–activity relationships of these dual EGFR/HER2 pyrrolotriazine kinase inhibitors and expand the potential for further lead optimization, we prepared analogues of **1** where the C-6 ester function and the C-5 substitutent are transposed, e.g., **2** and **3**. This report describes the synthesis and the EGFR/HER2 kinase inhibition of some representative examples of these pyrrolotriazine 5-esters. It also details a convenient, one-pot synthesis of the pyrrole 2,3-diesters that are synthetic precursors of pyrrolotriazines **3**.

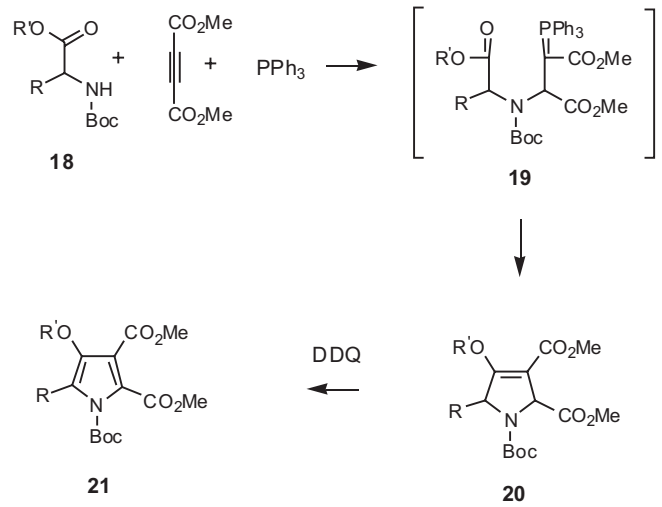


1 R = CO_2R'', R' = alkyl
2 R = alkyl, R' = CO_2R''
3 R = alkoxy, R = CO_2R''

Results and discussion

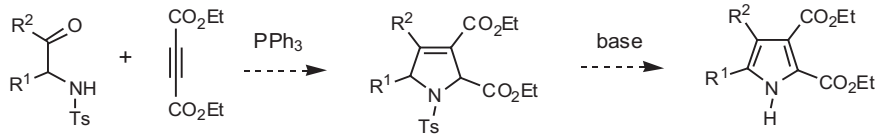
Preparation of the 6-methyl-5-ester **15** began with the known pyrrole **4** (5) and is outlined in Scheme 1. The pyrrole was converted to its *N*-amino derivative (**6**) by treatment with sodium hydride and monochloramine (6). Cyclization of **6** in hot formamide to the pyrrolotriazine-4-one (**8**) was followed by treatment with $POCl_3$ in refluxing toluene to give the 4-chloropyrrolotriazine (**10**). The 1-(3-fluorobenzyl)-1*H*-indazol-5-amino group was chosen as the lipohilic C-4 substituent and was introduced by reaction of **10** with **13** in the presence of base. The resulting methyl ester **14** was then converted to the ethyl ester **15** to enable a direct comparison of its biological activity with that of the transposed ethyl ester analogue (**17**).

Scheme 2.



The preparation of 6-alkoxy pyrrolotriazine analogs **3** required access to pyrroles that have an alkoxy group at C-4, e.g., **5**. A novel synthesis of such pyrroles has been reported (7) and is outlined in Scheme 2. The readily available N-Boc derivatives of α-amino acid esters **18** were found to react with dimethyl acetylenedicarboxylate and triphenylphosphine to give 3-pyrrolines **20** by way of the stabilized ylide **19**. These pyrrolines were isolated and then could be oxidized to pyrroles **21** by heating with DDQ. We explored the potential one-pot version of this procedure that is outlined in Scheme 3. It was thought that the *N*-tosyl derivative of α-amino acid esters **22** would similarly react with triphenyl phosphine and an acetylenedicarboxylate to form pyrrolines **23** that could be treated directly with base to eliminate toluenesulfinic acid and give the desired pyrroles **24**. A similar base-promoted elimination of toluenesulfinic acid from a *N*-tosyl pyrroline intermediate has been reported (8) to generate the corresponding pyrrole.

Scheme 3.



22 **23** **24**

Table 1. Conversion of sulfonamides **22** to pyrroles.

Entry	22	R^1	R^2	Pyrrole (yield, %)
1	**a**	H	OCH_3	**5** (82)
2	**b**	H	$OCH_2CH_2OCH_3$	**24a** (76)
3	**c**	CH_3	OCH_3	**24b** (54)
4	**d**	Ph	OCH_3	**24c** (68)
5	**e**	CH_2CH_2O		**24d** (7)
6	**f**	H	4-$CH_3OC_6H_5$	**24e** (94)
7	**g**	H	CH_3	**24f** (80)
8	**h**	H	$CH_2CH_2CO_2CH_3$	**24g** (71)

Note: Reaction conditions: **22** (1 equiv.), PPh_3 (1.25 equiv.), diethyl acetylenedicarboxylate (1.2 equiv.), dioxane, 10 °C to room temperature, 1 h; reflux 16 h; DBU (2.0 equiv.), 90 °C, 2 h.

Table 2. EGFR and HER2 kinase inhibition.

	IC_{50} (μmol/L)[a,b]	
Compound	EGFR	HER2
15	0.31	0.20
16	>1	>1
17	0.47	0.63

[a]Recombinant HER2 cytoplasmic sequence is expressed in Sf9 insect cells as an untagged protein and purified by ion-exchange chromatography. HER2 kinase activity is measured under the same conditions as for EGFR. See refs. 3 and 9 for assay conditions.

[b]IC_{50} values are reported as the mean of at least three determinations. Variability around the mean value was <15%.

The proposed reaction was examined with toluenesulfonamide derivatives of α-amino acid esters of glycine, alanine, phenylglycine, and α-amino butyrolactone (**22a**–**22d**, Table 1, entries 1–5) that were prepared from commercially available material by the Fischer esterification of *N*-tosyl amino acids or by treatment of the α-amino acid esters or lactone with *p*-toluenesulfonyl chloride in the presence of base. The derivatives were indeed found to react with diethyl acetylenedicarboxylate and triphenyl phosphine in refluxing dioxane to give the *N*-tosyl pyrroline intermediates **23** (confirmed by LC–MS analysis of the reaction mixture). DBU was then added and the reaction was heating at 90 °C to effect the elimination of toluenesulfinic acid. Good yields (82% to 54%) of the pyrroles **5** and **24a** to **24c** were obtained. A low yield (7%) of the fused furopyrrole **24d** was obtained. LC–MS analysis of the initial cyclization reaction mixture indicated the presence of the desired furopyrroline **23e** together with other products that were not isolated or identified. In this case, competing side reactions are most likely seen because of the additional strain that is encountered in the transition state that leads to **23e**.

To further explore the scope of this reaction, the sulfonamide derivatives of some alkyl and aryl α-aminoketones (**22f**–**22h**) were prepared and examined as substrates (Table 1, entries 6–8). Good yields (94% to 71%) of the pyrroles **24e**–**24g** were obtained in all cases.

With a convenient synthesis of 4-alkoxy pyrrole-2,3-dicarboxylic acid diesters in hand, an example of a pyrrolotriazine 5-ester with an alkoxy group at C-6 was made. The 6-methoxy pyrrolotriazine (**16**) was prepared from **5** using the same sequence of reactions that were used to make **15** (Scheme 1): N-amination of pyrrole **5**; cyclization of **7** in formamide; formation of the chloroimidate **9**; and final attachment of the 1-(3-fluorobenzyl)-1*H*-indazol-5-amino side chain. The 6-ester analogue (**17**) was made for comparison purposes from the known (4) 4-chloropyrrolotriazine intermediate (**12**).

Data for the inhibition of the EGFR and HER2 kinases by **15**–**17** is show in Table 2. The directly transposed analogue (**15**) was found to be at least as potent a dual kinase inhibitor as **17**, while the 6-ether analogue (**16**) was less potent. Since the 5-ester group in **15** is well-suited for functional group modifications that could improve biochemical potency and cellular activity, **15** became the focus of further structure activity and lead optimization studies. These results will be reported in the future.

Experimental section

Methyl 6-methyl-4-oxo-3,4-dihydropyrrolo[1,2-*f*][1,2,4]-triazine-5-carboxylate (8)

A mixture of dimethyl 4-methyl-1*H*-pyrrole-2,3-dicarboxylate (5) (**4**, 1.0 g, 5.1 mmol) and NaH (236 mg, 60% dispersion in oil, 1.3 equiv.) in dry DMF (2 mL) was stirred at room temperature for 30 min. A solution of monochloramine (6) (66 mL, 0.1 mol/L in diethyl ether, 1.3 equiv.) was added with vigorous stirring. After 2 h, the reaction was cooled in an ice-water bath and an aqueous solution of $Na_2S_2O_3$ (20 mL, 1.0 N) was added with stirring. This was diluted with water (200 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent followed by silica gel column chromatography (gradient elution with mixtures of hexane containing 0%– 50% EtOAc) afforded dimethyl 1-amino-4-methyl-1*H*-pyrrole-2,3-dicarboxylate (**6**, 845 mg, 79% yield) as an oil. ^{1}H NMR (MeOH-d_4, 500 MHz, ppm) δ: 2.08 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 6.69 (s, 1H). A suspension of **6** (805 mg, 3.80 mmol) in formamide (8 mL) was heated at 170 °C for 2 h under a N_2 atmosphere. After cooling to room tempera-

ture, this was poured into water (20 mL) and left stirring overnight. The product was collect by filtration, washed with water and Et_2O, and then dried (590 mg, 75%). ^{1}H NMR (MeOH-d_4, 300 MHz, ppm) δ: 2.30 (s, 3H), 3.87 (s, 3H), 7.32 (s, 1H), 7.72 (s, 1H). HPLC purity: 93%. MS (ESI) *m*/*z*: 208 (M + H).

Methyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-6-methylpyrrolo[1,2-*f*][1,2,4]triazine-5-carboxylate (14)

A mixture of methyl 6-methyl-4-oxo-3,4-dihydropyrrolo-[1,2-*f*][1,2,4]triazine-5-carboxylate (**8**, 1.00 g, 4.83 mmol), $POCl_3$ (0.54 mL, 1.2 equiv.) and diisopropylethylamine (0.67 mL, 0.8 equiv.) in dry toluene (15 mL) was heated at reflux for 5 h. After cooling to room temperature, the reaction was poured into a saturated aqueous solution of $NaHCO_3$ with vigorous stirring. The organic phase was separated, washed with additional satd. aq. $NaHCO_3$ solution and dried (Na_2SO_4). Removal of the solvent followed by silica gel chromatography (elution with dichloromethane) afforded methyl 4-chloro-6-methylpyrrolo[1,2-*f*][1,2,4]-triazine-5-carboxylate (**10**, 777 mg, 72%) as a solid. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ: 2.45 (s, 3H), 3.95 (s, 3H), 7.68 (s, 1H), 8.26 (s, 1H). MS (ESI) *m*/*z* 226 (M + H). A mixture of **10** (1.29 g, 5.06 mmol), 1-(3-fluorobenzyl)-1*H*-indazol-5-amine (**13**, 1.46 g, 1.2 equiv.) and $NaHCO_3$ (2.13 g, 5 equiv.) in dry CH_3CN (50 mL) was left stirring at room temperature for 4 h. The product was collected by filtration, washed with water, and dried (2.06 g, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 2.43 (s, 3H), 3.97 (s, 3H), 5.59 (s, 2H), 6.95 (m, 3H), 7.34 (m, 3H) 7.65 (m, 1H), 8.06 (s, 2H), 8.40 (s, 1H). MS (ESI) *m*/*z*: 431 (M + H). HRMS (ESI) calcd. for $C_{23}H_{20}N_6O_2F$: 431.1737; found: 461.1653.

Ethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-6-methylpyrrolo[1,2-*f*][1,2,4]triazine-5-carboxylate (15)

Transesterification (EtOH, K_2CO_3) of **14** gave the product: ^{1}H NMR ($CDCl_3$, 500 MHz) (ppm) δ: 1.44 (t, *J* = 7 Hz, 3H), 4.42 (q, *J* = 7 Hz, 2H), 5.58 (s, 2H), 6.85 (m, 1H), 6.94 (m, 2H), 7.27 (m, 3H), 7.63 (m, 1H), 8.05 (s, 2H), 8.39 (s, 1H). 7.65 (m, 1H), 8.06 (s, 2H), 8.40 (s, 1H). MS (ESI) *m*/*z*: 445 (M + H). HRMS (ESI) for $C_{24}H_{22}N_6O_2F$ calcd.: 445.1788; found: 445.1778.

2-Methoxyethyl 2-(4-methylphenylsulfonamido)acetate (22b)

A mixture of 2-(4-methylphenylsulfonamido)acetic acid (5.0 g, 21.8 mmol), 2-methoxyethanol (10.0 g, 6 equiv.), and *p*-toluenesulfonic acid (0.2 g, 0.05 equiv.) in xylene (50 mL) was heated at 150 °C for 10 h. After cooling to room temperature, this was washed with satd. aq. $NaHCO_3$ solution and dried (Na_2SO_4). Removal of the solvent followed by silica gel chromatography (step gradient elution with mixtures of hexane containing 5%–30% EtOAc) afforded the product as an oil (5.3 g, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 2.37 (s, 3H), 3.28 (s, 3H), 3.47 (t, *J* = 4.5 Hz, 2H), 3.76 (d, *J* = 5.4 Hz, 2H), 4.12 (t, *J* = 4.5 Hz, 2H), 5.38 (m, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H). HPLC purity: 92%. MS (ESI) *m*/*z*: 320 (M + H).

Methyl 2-(4-methylphenylsulfonamido)propanoate (22c)

Triethylamine (1.53 mL, 2 equiv.) was added dropwise to an ice-cooled mixture of DL-alanine methyl ester hydrochloride (768 mg, 5.5 mmol) and toluenesulfonyl chloride (1.05 g, 1 equiv.) in dry dichloromethane (12 mL). After 1 h, the bath was removed and after a further 2 h, the reaction was filtered. The filtrate was washed with water, dried (Na_2SO_4), and the solvent removed. This left the crude product as an oil (1.26 g). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ: 1.35 (d, 3H, *J* = 7 Hz), 2.39 (s, 3H), 3.51 (s, 3H), 3.96 (m, 1H), 5.33 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H). HPLC purity: 93%. MS (ESI) *m*/*z*: 228 (M + H).

(*S*)-Methyl 2-(4-methylphenylsulfonamido)-2-phenylacetate (22d)

Similarly, (*S*)-(+)-phenylglycine methyl ester hydrochloride was converted to the product. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ: 2.38 (s, 3H), 3.56 (s, 3H), 5.05 (d, *J* = 8 Hz, 1H), 5.63 (d, *J* = 8 Hz, 1H), 7.24 (m, 7H), 7.62 (d, *J* = 8.0 Hz, 2H). HPLC purity: 92%. MS (ESI) *m*/*z*: 320 (M + H).

4-Methyl-*N*-(2-oxo-tetrahydrofuran-3-yl)benzenesulfonamide (22e)

Similarly, 3-amino-dihydrofuran-2(3*H*)-one hydrobromide was converted to the product. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ: 2.29 (m, 1H), 2.43 (s, 3H), 2.70 (m, 1H), 3.89 (m, 1H), 4.18 (m, 1H), 4.20 (t, *J* = 9.0 Hz, 1H), 5.15 (m, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J*= 8.5 Hz, 2H). HPLC purity: 90%. MS (ESI) *m*/*z*: 256 (M + H).

1-(4-Methoxyphenyl)-2-(4-methylphenylsulfonamido)-ethanone (22f)

Similarly, 2-amino-1-(4-methoxyphenyl)ethanone hydrochloride was converted to the product (solid). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 2.38 (s, 3H), 3.85 (s, 3H), 4.38 (d, 2H, (d, 1H, *J* = 4.5 Hz), 5.66 (m, 1H), 6.91 (d, 2H), 7.26 (d, 2H), 7.79 (m, 4H). HPLC purity: 90%. MS (ESI) *m*/*z*: 320 (M + H).

4-Methyl-*N*-(2-oxopropyl)benzenesulfonamide (22g)

Tetrapropylammonium perruthenate (70 mg, 0.1 equiv.) was added to a stirred suspension of *N*-(2-hydroxypropyl)-4-methylbenzenesulfonamide (458 mg, 2.0 mmol), *N*-methylmorpholine *N*-oxide (35 mg, 1.5 equiv.), and powdered, dry 4 Å molecular sieves (1.6 g) in dry CH_3CN. After 20 min, the CH_3CN was removed under vacuum and the residue was dissolved in dichloromethane and filtered through a short pad of silica gel. The solvent was removed from the filtrate and the product was isolated by radial silica gel chromatography (step gradient elution with mixtures of hexane containing 0%–30% ethyl acetate) as a solid (159 mg, 35%). ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ: 2.09 (s, 3H), 2.39 (s, 3H), 3.83 (d, *J* = 5 Hz, 2H), 5.35 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H). HPLC purity: 84%. MS (ESI) *m*/*z*: 228 (M + H).

Methyl 5-(4-methylphenylsulfonamido)-4-oxopentanoate (22h)

Methyl 5-amino-4-oxopentanoate hydrochloride was converted to the product as described for **22c**. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ: 2.41 (s, 3H), 2.60 (m, 4H), 3.62 (s, 3H), 2.89 (d, *J* = 5 Hz, 2H), 5.30 (m, 1H), 7. 28 (d, *J* = 8.0 Hz,

2H), 7.71 (d, *J* = 8.0 Hz, 2H). HPLC purity: 93%. MS (ESI) *m*/*z*: 300 (M + H).

General procedure for the preparation of 5 and 24a–24g

A mixture of the sulfonamide (**22a**–**22h**) (1.0 equiv.) and triphenylphosphine (1.25 equiv.) in dry dioxane (0.5 mol/L) under a N_2 atmosphere was cooled in an ice-water bath. Diethyl acetylenedicarboxylate (1.2 equiv.) was added dropwise over 5 min and the bath was removed. After 1 h, the reaction was brought to reflux and left heating overnight. The temperature was reduced to 90 °C and DBU (2.0 equiv.) was added. After 2 h, the solvent was removed and the product was isolated by silica gel column chromatography eluting with mixtures of hexane containing 0%–25% ethyl acetate.

Diethyl 4-methoxy-1*H*-pyrrole-2,3-dicarboxylate (5)

^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 1.28 (m, 6H), 3.71 (m, 3H), 4.28 (m, 4H), 6.43 (d, *J* = 2.93 Hz, 1H), 9.58 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 164.2, 160.4, 148.5, 119.4, 109.9, 104.1, 61.1, 61.0, 58.7, 14.3. HRMS (ESI) calcd. for $C_{11}H_{14}NO_5$: 240.0872; found: 240.0875.

Diethyl 4-(2-methoxyethoxy)-1*H*-pyrrole-2,3-dicarboxylate (24a)

^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.24 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 3.34 (s, 3H), 3.61 (m, 2H), 3.95 (m, 2H), 4.24 (m, 4H), 6.45 (d, *J* = 3.1 Hz, 1H), 9.69 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 164.3, 160.4, 146.9, 119.1, 110.9, 106.7, 71.7, 71.1, 60.9, 60.4, 59.5, 14.2, 14.0. HRMS (ESI) calcd. for $C_{13}H_{19}NO_6$: 285.1134; found: 284.1131.

Diethyl 4-methoxy-5-methyl-1*H*-pyrrole-2,3-dicarboxylate (24b)

^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.31 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 2.20 (s, 3H), 3.77 (s, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 9.42 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 164.9, 161.0, 143.5, 122.8, 115.4, 114.1, 62.7, 61.0, 60.8, 14.3, 14.2, 9.5. HRMS (ESI) calcd. for $C_{12}H_{16}NO_5$: 254.1028; found: 254.1021.

Diethyl 4-methoxy-5-phenyl-1*H*-pyrrole-2,3-dicarboxylate (24c)

^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.33 (t, *J* = 7.2 Hz, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.39 (q, *J* = 7.0 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.69 (d, *J* = 7.7 Hz, 2H), 9.18 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 164.7, 160.8, 143.8, 129.8, 128.9, 127.8, 125.9, 124.7, 117.4, 115.4, 62.2, 61.3, 61.2, 14.3, 14.2. HRMS (ESI) calcd. for $C_{17}H_{18}NO_5$: 316.1185; found: 316.1179.

Diethyl 3,4-dihydro-2*H*-*furo*[3,2-*b*]pyrrole-5,6-dicarboxylate (24d)

^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.35 (m, 6H), 3.12 (t, *J* = 8.4 Hz, 2H), 4.32 (m, 4H), 4.96 (t, *J* = 8.2 Hz, 2H), 9.20 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 162.7, 160.3, 153.3, 122.3, 121.6, 103.9, 78.4, 61.0, 60.7, 26.2, 14.4, 14.3. HRMS (ESI) calcd. for $C_{12}H_{16}NO_5$: 254.1029; found: 254.1038.

Diethyl 4-(4-methoxyphenyl)-1*H*-pyrrole-2,3-dicarboxylate (24e)

^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.28 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 3.80 (s, 3H), 4.32 (m, 4H), 6.88 (m, 2H), 6.94 (d, *J* = 3.1 Hz, 1H), 7.32 (m, 2H), 9.33 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 166.8, 160.4, 158.8, 128.8, 126.3, 125.8, 121.3, 120.4, 120.0, 114.1, 61.4, 61.0, 55.3, 14.3, 14.2. HRMS (ESI) calcd. for $C_{17}H_{19}NO_5$: 316.1185; found: 316.1178.

Diethyl 4-methyl-1*H*-pyrrole-2,3-dicarboxylate (24f)

^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.29 (t, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 2.12 (s, 3H), 4.27 (m, 2H), 4.31 (m, 2H), 6.63 (d, *J* = 2.8 Hz, 1H), 9.55 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 165.8, 160.5, 122.1, 121.9, 120.7, 120.5, 60.9, 60.7, 14.3, 14.2, 10.9. HRMS (ESI) calcd. for $C_{11}H_{15}NO_4$: 224.0922; found: 224.0913.

Diethyl 4-(3-methoxy-3-oxopropyl)-1*H*-pyrrole-2,3-dicarboxylate (24g)

^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.25 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 2.53 (t, *J* = 7.5 Hz, 3H), 2.83 (t, *J* = 7.63 Hz, 2H), 3.58 (s, 3H), 4.26 (m, 4H), 9.83 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 173.6, 165.5, 160.4, 125.1, 122.1, 120.4, 119.9, 60.9, 60.8, 51.6, 35.1, 21.2, 14.3, 14.2. HRMS (ESI) calcd. for $C_{14}H_{19}NO_6$: 298.1291; found: 298.1277.

Ethyl 6-methoxy-4-oxo-3,4-dihydropyrrolo[1,2-*f*][1,2,4]-triazine-5-carboxylate (9)

A solution of diethyl 4-methoxy-1*H*-pyrrole-2,3-dicarboxylate (**5**, 2.48 g, 10.3 mmol) in dry CH_3CN (10 mL) was added to an ice-cooled suspension of NaH (535 mg, 60% dispersion in oil, 1.3 equiv.) in dry dimethyl formamide (20 mL) over 3 min. The bath was removed and the reaction was left stirring for 1 h after which it was cooled in an ice bath. A solution of monochloramine (135 mL, 0.1 mol/L in diethyl ether, 1.3 equiv.) was added with vigorous stirring. After 30 min, the bath was removed and the reaction was left stirring for 1.5 h. It was then cooled in an ice-water bath and worked up as described for **6**. Silica gel column chromatography (gradient elution with mixtures of hexane containing 0%–25% ethyl acetate) afforded diethyl 1-amino-4-methoxy-1*H*-pyrrole-2,3-dicarboxylate (**7**) as an oil (1.53 g, 58% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 1.30 (m, 6H), 3.70 (s, 3H), 4.27 (m, 4H), 5.4 (br s, 2H), 6.47 (s, 1H). MS (ESI) *m*/*z*: 257 (M + H). A suspension of **7** (880 mg, 3.44 mmol) in formamide (5 mL) was heated at 170 °C for 4 h under a N_2 atmosphere. This was worked up as described for **8** to give the product (514 mg, 63%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ: 1.25 (t, *J* = 7.2 Hz, 3H), 3.76 (s, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 7.44 (s, 1H), 7.91 (s, 1H). MS (ESI) *m*/*z*: 238 (M + H). HRMS (ESI) calcd. for $C_{10}H_{12}N_3O$: 238.0828; found: 238.0824.

Ethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-6-methoxypyrrolo[1,2-*f*][1,2,4]triazine-5-carboxylate (16)

A mixture of **9** (887 mg, 3.37 mmol), $POCl_3$ (0.79 mL, 1.5 equiv.), and diisopropylethylamine (0.59 mL, 1.0 equiv.) in dry toluene (12 mL) was heated at reflux for 5 h and then worked up as described for **10**. Silica gel radial chromatography (elution with DCM) afforded ethyl 4-chloro-6-

methoxypyrrolo[1,2-*f*][1,2,4]triazine-5-carboxylate (**11**, 458 mg, 53%) as a solid. MS (ESI) *m*/*z*: 256 (M + H). HRMS (ESI) calcd. for $C_{10}H_{11}N_3O_3Cl$: 256.0489; found: 256.0496. A mixture of **11** (1.30 g, 5.10 mmol), 1-(3-fluorobenzyl)-1*H*-indazol-5-amine (**13**, 1.25 g, 1.05 equiv.), and diisopropylethylamine (1.07 mL, 1.2 equiv.) in dry CH_3CN (45 mL) was heated at 70 °C overnight. The product was collected by filtration, washed with CH_3CN, and dried (2.15 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 1.43 (t, *J* = 6.9 Hz, 3H), 3.89 (s, 3H), 4.42 (q, *J* = 6.9 Hz, 2H), 5.57 (s, 2H), 6.84 (m, 1H), 6.94 (m, 2H), 7.14 (s, 1H), 7.26 (m, 2H) 7.60 (m, 1H), 8.04 (s, 1H), 8.08 (s, 1H), 8.38 (m, 1H). MS (ESI) *m*/*z*: 461 (M + H). HRMS (ESI) calcd. for $C_{24}H_{22}N_6O_3F$: 461.1737; found: 461.1726.

Ethyl 4-[1-(3-fluoro-benzyl)-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (17)

A 2 L three-neck flask was charged with ethyl 4-chloro-5-methyl-pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (4) (**12**, 54.0 g, 226 mmol) and acetonitrile (500 mL). To the resulting suspension was added 1-(3-fluoro-benzyl)-1*H*-indazol-5-ylamine (**13**, 54.5 g, 226 mmol) and diisopropylethyl amine (21.7 g, 214.7 mmol). The reaction was heated to 55 °C and became homogeneous after 10 min. After 18 h, it was cooled to 10 °C and filtered. The filter cake was washed with cold acetonitrile (2 × 250 mL) and dried under vacuum to afford the product as a white crystalline solid (76.3 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ: 1.39 (t, *J* = 7.2 Hz, 3H), 2.93 (s, 3H), 4.35 (q, *J* = 7.2 Hz, 2H), 5.59 (s, 2H), 6.86 (d, *J* = 9.3 Hz, 1H), 6.97 (m, 2H), 7.26 (ddd, *J* = 6.04, 8.24, 14.29 Hz, 1H), 7.35 (d, 1H, *J* = 8.80 Hz), 7.42 (br s, 1H), 7.49 (dd, 1H, *J* = 1.65, 8.80 Hz), 7.91 (s, 1H), 8.00 (s, 1H), 8.07 (s, 1H), 8.09 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ: 164.5, 163.0 (d, *J* = 246 Hz), 154.9, 148.5, 139.1 (d, *J* = 5 Hz), 137.6, 133.8, 130.3, 131.2 (d, *J* = 7 Hz), 124.6, 123.5, 122.7, 121.9 (2C), 115.4, 115.3, 114.8 (d, *J* = 20 Hz), 114.1 (d, *J* = 22 Hz), 113.4, 109.7, 60.2, 52.6, 14.4, 11.9. MS (ESI) *m*/*z*: 444 $(M + H)^+$. HRMS (ESI) calcd. for $C_{24}H_{22}FN_6O_2$: 445.171; found: 445.1805. Anal calcd. for $C_{24}H_{21}FN_6O_2$: C 64.85, H 4.76, N 18.90; found: C 64.62, H 4.73, N 18.85.

Conclusion

In summary, pyrrolotriazine analogs with an ester function at C-5 were made and evaluated as dual inhibitors of EGFR and HER2 kinases. The 5-ester 6-methyl analog (**15**) showed kinase inhibition that was at least comparable to that seen for the 6-ester 5-methyl analogue (**17**). It became the focus of further structure activity and lead optimization studies and these results will be reported in the future. In addition, a general, one-pot procedure for the synthesis of C-4 substituted pyrrole-2,3-diesters from readily available *N*-tosyl derivatives of α-amino acid esters and α-amino ketones was developed.

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