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NEW SYNTHESIS OF 3*H*-BENZO[*b*]THIOPHEN-2-ONES

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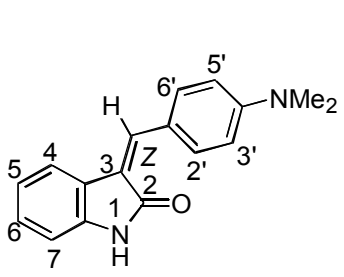
Abstract – The reaction of 2-methylthiophenol with sodium hydride and *N,N*-diethylcarbamyl chloride in THF afforded *N,N*-diethylthiocarbamic acid *S*-*o*-tolyl ester in 97% yield. The ester was subsequently treated with LDA and various aromatic aldehydes to provide new 3-substituted derivatives of (alkyliden-1-yl)-3*H*-benzo[*b*]thiophen-2-ones. The *Z* isomer was formed as major product with smaller amounts of the *E* isomer. The structure of (*Z*)-3-(thiophen-2-yl)methylidenyl-3*H*-benzo[*b*]thiophen-2-one was confirmed by X-Ray crystallography.

3-Substituted (alkyliden-1-yl)-3*H*-benzo[*b*]indolin-2-ones (**1-3**) exhibit inhibitory properties against



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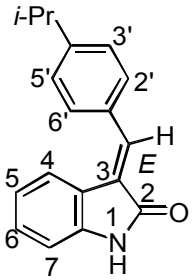

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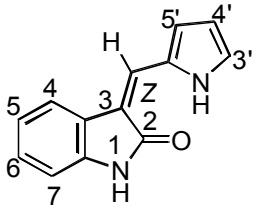
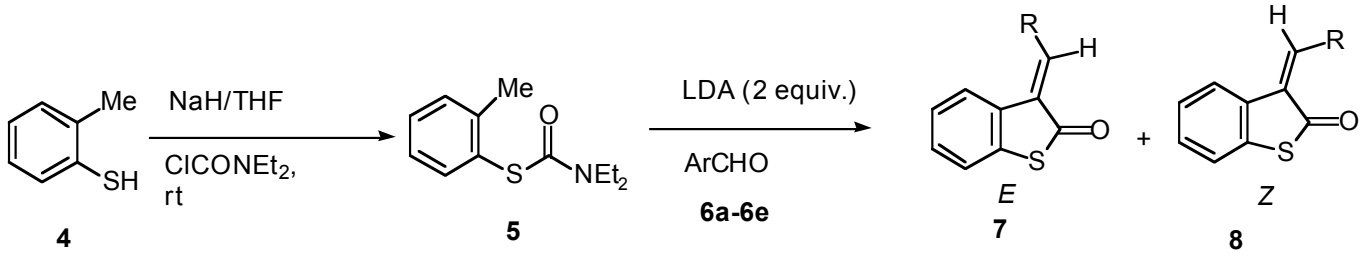


3

various receptor tyrosine kinases (RTKs).[1] Compounds (**1**) and (**3**) are potent and selective inhibitors of the vascular endothelial growth factor (VEGF) [fetal liver kinase-1 (*Flk-1*)]RTKs, whereas **2** is a nonselective inhibitor of RTK. We have expanded the chemical diversity of this structural type by developing a new strategy towards the synthesis of 3-substituted (alkyliden-1-yl)-3*H*-benzo[*b*]thiophen-2-ones in which the nitrogen atom has been replaced by a sulfur atom. The synthesis, shown in Scheme 1, involved the conversion of commercially available 2-methylthiophenol (**4**) to its *N,N*-dimethylthiocarbamate ester (**5**)[2,3] using NaH and THF at room temperature. The yield was excellent (>97%). Previous

syntheses of thiocarbamates involved longer routes and more drastic conditions, and the yields were variable.[4] The *N,N*-dimethylthiocarbamate (**5**) was subsequently treated with two equivalents of LDA at



Scheme 1

–30 ^{0}C followed by the addition of the aldehyde (**6a-e**). The results listed in Table 1 show that the Z diastereomers (**8a-e**) were obtained as major products in good yields along with smaller amounts of the corresponding *E* diastereomers (**7a-e**). The *E* and *Z* mixtures were separated by silica gel thick layer chromatography and their structures determined by ^{1}H and ^{13}C NMR spectroscopy. Their assignments were based on their respective ^{1}H NMR spectrum with the *Z* isomers having olefinic proton chemical shifts around δ 7.8 ppm and the *E* isomers having chemical shifts around δ 7.5 ppm. These assignments were made using spectral data of similarly structure 3-substituted indol-2-ones as reference compounds.[1] We interpret the higher chemical shift of the *Z*- isomer to be due to the deshielding effect of the aromatic ring located near the olefinic proton of the *Z*-isomer. The preference for the *Z* configuration is probably due to steric interference between the ring at C-3 and the 4-H on the phenyl ring in the *E* configuration. The configuration of the *Z*-isomer (**8b**), shown in Table 1 (Entry 2), was further confirmed by single crystal X-Ray crystallography from which an ORTEP drawing was obtained and shown in Figure 1. This configuration is further stabilized by electrostatic interaction between the C=O and S shown in Figure 2.

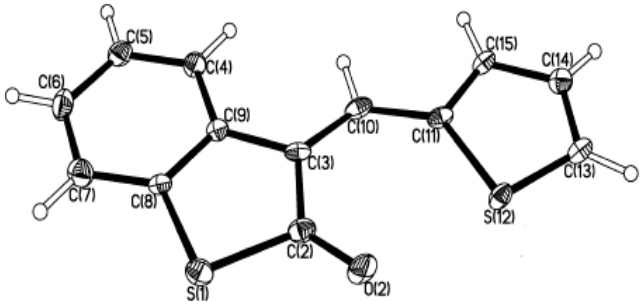
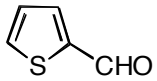
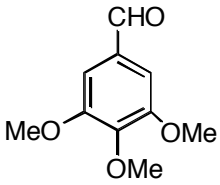
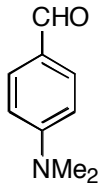
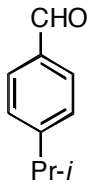


Figure 1 ORTEP structure of compound (**8b**)

The mechanism shown in Scheme 2 most likely involves the deprotonation of the 2-methyl group of ester (**5**) by LDA to give the anion (**9**) which undergoes the cyclization to 2-oxo-2,3-dihydrobenzo[*b*]-thiophene (**10**). Deprotonation of the α CH bond of **10** followed by condensation with aldehyde (**6**) gives

Table 1 Yields of **7** and **8** from the Reaction of **5** with Various Aldehydes (**6a-e**).

Entry	Aldehyde	Yield (%), overall	Yield (%), *E* isomer	Yield (%) *Z* isomer
1	PhCHO **6a**	89	18 **7a**	71 **8a**
2	 **6b**	92	trace **7b**	92 **8b**
3	 **6c**	87	17 **7c**	80 **8c**
4	 **6d**	88	26 **7d**	60 **8d**
5	 **6e**	95	trace **7e**	95 **8e**

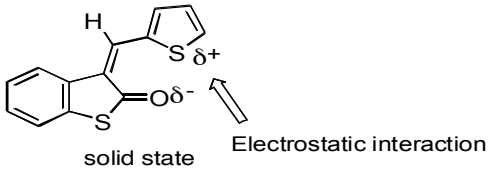
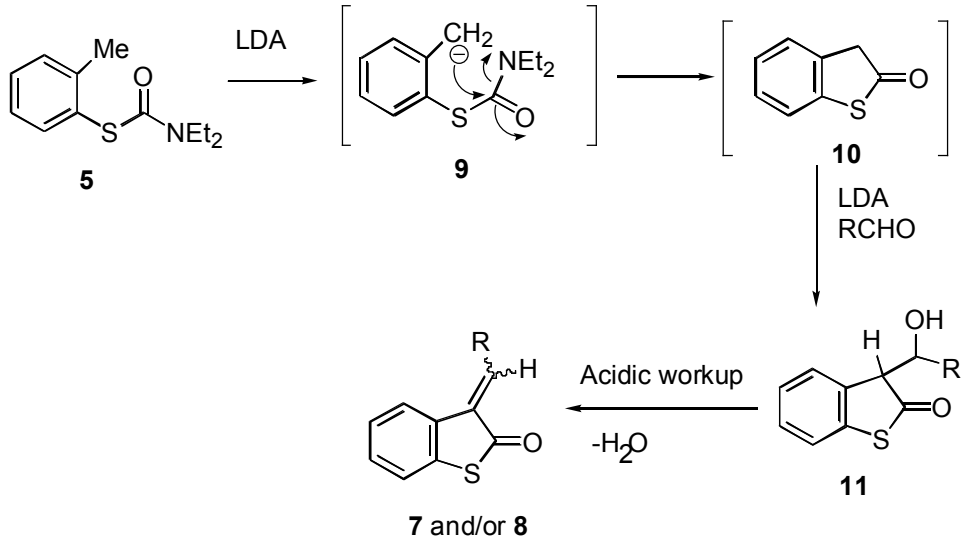


Figure 2

the adduct (**11**), which upon acidic work up is converted to **7** and/or **8**. The intermediacy of 2-oxo-2,3-dihydrobenzo[*b*]thiophene (**10**) was confirmed by preparing it in good yield (78%) from the reaction of LDA and the ester (**5**) in the absence of an aldehyde. Compound (**10**), obtained in this way, was subsequently treated with LDA and benzaldehyde to give **7a** and **8a**.



Scheme 2

In conclusion, we have reported a one- step, high-yield synthesis of 3-substitued (alkyliden-1-yl)-3*H*-benzo[*b*]thiophen-2-ones which compares well with the few previously reported[5-8] syntheses which require three steps and give 2-oxothiophenes in only modest yields.

EXPERIMENTAL

General Data: Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. IR spectra were recorded on a Nicolet Magna-IRTM 550 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 Multinuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard.

Optimized Procedure for the Synthesis of *N,N*-Diethylthiocarbamic Acid *S*-*o*-Tolyl ester (5). To a well-stirred solution of NaH (60%, suspended in paraffin, 0.6 g, 24 mmol) and THF(10 mL) kept under argon atmosphere at rt 2-methylthiophenol (1 g, 8 mmol) in THF (5mL) was slowly added through needle syringe system. The reaction mixture was stirred for 1 h and *N,N*-diethylcarbamyl chloride (2.2 mL, 16 mmol) in THF (5 mL) was added slowly using the same procedure. Then the reaction mixture was kept overnight and cooled to 0 ^{0}C and ice water was added to it. THF was distilled off and the crude product was extracted with dichloromethane, washed with water (3x100 mL), and dried (over Na_2SO_4). Evaporation of solvent under reduced pressure provided the crude product which was purified by silica

gel column chromatography using 30% ethyl acetate–hexane as eluent. This compound was obtained as an oil, yield, 1.7 g (95%), IR (neat) ν1659 cm^{-1}. H NMR ($CDCl_3$) δ 1.31 (t, *J* = 6.4 Hz, 3H, -CH_2-C$\underline{H}_3$), 1.44 (t, *J* = 6.4 Hz, 3H, -CH_2-C$\underline{H}_3$), 2.43 (s, 3H, -CH_3), 3.90 (q, *J* = 6.4 Hz, 2H, -C$\underline{H}_2$-CH_3), 4.05 (q, *J* = 6.4 Hz, 2H, -C$\underline{H}_2$-CH_3), 7.28 (dd, *J* = 3.5 Hz, 8.0 Hz, 1 H, Ar-H-5), 7.36 (d, *J* = 8.0 Hz, 1H, Ar-H-3), 7.41 (dd, *J* = 8.0 Hz, 3.5 Hz, 1H, Ar-H-4), 7.45 (d, *J* = 8.0 Hz, 1H, Ar-H-6). ^{13}C NMR ($CDCl_3$): δ 13.78, 14.29, 21.27, 42.86, 126.77, 128.78, 130.15, 130.94, 137.55, 143.39, 165.61. *Anal.* Calcd for $C_{12}H_{17}NOS$: C, 64.53; H, 7.67; N; 6.27. Found: C, 64.59; H, 7.68; N, 6.30.

General Procedure for the Synthesis of 3-(Alkyliden-1-yl)-3*H*-benzo[*b*]thiophen-2-ones (7, 8). To a well stirred solution of THF (10 mL) and BuLi [1.6 mL of 1.5 (M) solution in hexane] kept at –78 °C under argon atmosphere, diisopropylamine (0.45 g, 0.6 mL, 2.5 equiv) was added through needle syringe system. The reaction mixture was allowed to warm to –20 °C and was kept for 45 min at that temperature. A solution of *N,N*-diethylthiocarbamic acid *S*-*o*-tolyl ester (0.37 g, 1.6 mmol) in THF (3 mL) was slowly added at the same temperature followed by benzaldehyde (0.2 g, 1.6 mmol) in THF (3 mL). The reaction mixture was stirred for 1 h at –20 °C and allowed to reach ambient temperature and kept overnight. Then the reaction mixture was cooled to 0 °C and 5% HCl (10 mL) was added to it, stirred for 15 min, extracted with CH_2Cl_2 (100 mL), washed with water (3x100 mL), and dried (Na_2SO_4). Evaporation of solvent provided the crude product, which was purified by silica gel column chromatography using 20% ethyl acetate-hexane as the eluent. The spectral and physical properties of the products are shown below.

***(E)*-3-(Benzylidenyl)-3*H*-benzo[*b*]thiophen-2-one (7a)**

This compound was isolated as an oil, IR (neat) ν1617 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.10 (ddd, 1H, *J* = 2.1 Hz, 7.5 Hz, 7.6 Hz, Ar-H-6), 7.30 (dd, 2H, *J* = 7.6 Hz, 8.2 Hz, Ar-H-5′, H-3′), 7.51 (m, 6H, Ar-H-5, H-7, H-4′, H-2′, H-6′ and olefinic proton), 7.82 (dd, 1H, *J* = 1.5 Hz, 7.8 Hz, Ar-H-4). ^{13}C NMR ($CDCl_3$) δ 124.10, 125.21, 126.12, 127.08, 128.71, 129.12, 129.32, 130.10, 130.21, 132.04, 134.23, 138.71, 187.01. *Anal.* Calcd for $C_{15}H_{10}OS$: C, 75.60; H, 4.23. Found: C, 75.68; H, 4.40.

(*Z*)-3-(Benzylidenyl)-3*H*-benzo[*b*]thiophene-2-one (8a)

This compound was obtained as an oil, IR (neat) ν 1615 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.02 (ddd, 1H, *J*= 2.8 Hz, 7.4 Hz, 7.8 Hz, Ar-H-6), 7.31 (dd, 2H, *J* = 7.5 Hz, 7.8 Hz, Ar-H-5′, H-3′), 7.51 (m, 5H, Ar- H-5, H-7, H-4′, H-2′, H-6′), 7.82 (s, olefinic proton) 7.91 (dd, 1H, *J*=1.5 Hz, 7.8 Hz, Ar-H-4). ^{13}C NMR ($CDCl_3$) δ 123.90, 124.68, 125.93, 128.57, 129.21, 129.27, 130.21, 130.31, 131.99, 134.19, 138.86, 186.01. *Anal.* Calcd for $C_{15}H_{10}OS$: C, 75.60; H, 4.23. Found: C, 75.58; H, 4.30.

(*Z*)-3-(Thiophen-2-ylmethylidenyl]-3*H*-benzo[*b*]thiophen-2-one (8b)

This compound was obtained as yellow solid (yellow needles from CH_2Cl_2/hexanes, mp 143-145 °C, IR (KBr) ν 1650 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 4H, Ar-H-4, H-5, H-6 and H-7), 7.41 (d, 1H, *J*=7.4 Hz, Ar-H-4′), 7.60 (d, 1H, *J*=7.4 Hz, Ar-H-3′), 7.72 (d, 1H, *J* = 4.9 Hz, Ar-H-5′). 7.81 (s, 1H, olefinic proton).

^{13}C NMR ($CDCl_3$) δ 120.61, 123.66, 126.13, 126.99, 127.99, 129.06, 130.26, 133.39, 135.09, 135.43, 137.94, 139.99, 192.73. *Anal.* Calcd for $C_{13}H_8OS_2$: C, 63.90; H, 3.30. Found: C, 64.00; H, 3.31.

(*E*)-3-(3,4,5-Trimethoxybenzylidenyl)-3*H*-benzo[*b*]thiophen-2-one (7c)

This compound was obtained as a light yellow solid (yellow crystals from CH_2Cl_2/hexanes), mp 70-72 °C, IR (KBr) ν 1652 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 3.90 (s, 3H, -OMe), 3.91 (s, 3H, -OMe), 3.96 (s, 3H, -OMe), 6.92 (s, 2H, Ar-H-2$^/$, H-6$^/$), 7.40 (m, 2H, Ar-H-6, H-7), 7.51 (s, 1H, olefinic proton), 7.80 (m, 2H, Ar-H-4, H-5). ^{13}C NMR ($CDCl_3$) δ 56.60, 61.52, 106.71, 123.52, 123.80, 124.90, 129.31, 129.72, 130.33, 133.41, 136.41, 139.70, 140.04, 152.90, 153.91, 195.1. *Anal.* Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91. Found C, 65.87; H, 5.31.

(*Z*)-*3*-(3,4,5-Trimethoxybenzylidenyl]-3*H*-benzo[*b*]thiophen-2-one (8c)

This compound was obtained as a yellow solid (yellow crystals from CH_2Cl_2/hexanes), mp 122-124 °C. IR (KBr) ν 1652 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H, -OMe), 3.90 (s, 3H, -OMe), 3.96 (s, 3H, -OMe), 6.86 (s, 2H, Ar-H-2$^/$, H-6$^/$), 7.35 (m, 2H, H-6, H-7), 7.82 (s, 1H, olefinic proton), 7.75 (m, 2H, Ar-H-4, H-5). ^{13}C NMR ($CDCl_3$) δ 56.63, 61.42, 106.82, 123.41, 123.96, 124.80, 129.28, 129.64, 130.29, 130.5, 133.41, 136.37, 139.69, 140.04, 152.85, 153.80, 194.84. *Anal.* Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.92. Found C, 65.9; H, 5.13.

(*E*)-3-(4-*N*,*N*-Dimethylaminobenzylidenyl)-3*H*-benzo[*b*]thiophen-2-one (7d)

This compound was obtained as an oil, IR (neat) ν 1652 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.21 (s, 6H, *N*-CH_3) 6.62 (d, 2H, *J* = 1.9 Hz, 7.8 Hz, Ar-H-5, H-6), 7.22 (dd, 1H, *J* = 1.9 Hz, 7.8 Hz, Ar-H-7), 7.31 (s, 1H, olefinic), 7.60 (dd, 1H, *J* = 1.8 Hz, 7.8 Hz, Ar-H-4), 7.62 (d, 2H, *J* = 7.8 Hz, Ar-H-5$^/$, H-6$^/$), 8.21 (d, 2H, *J* = 7.8 Hz, Ar-H-2$^/$, H-3$^/$). ^{13}C NMR ($CDCl_3$) δ 41.41, 41.47, 112.10, 120.40, 123.48, 125.08, 125.74, 127.61, 128.11, 131.98, 132.90, 135.62, 136.04, 141.01, 141.70, 152.30, 194.5. *Anal.* Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98, Found C, 72.60; H, 5.43; N, 4.87. **(*Z*)-3-(4-*N*,*N*-Dimethylaminobenzylidenyl)-3*H*-benzo[*b*]thiophen-2-one (8d)**

This compound was obtained as a light red oil, IR (KBr) ν 1650 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.12 (s, 6H, *N*-CH_3), 6.70 (dd, 2H, *J* = 1.8 Hz, 7.6 Hz, Ar-H-5, H-6), 7.11 (dd, 1H, *J* = 1.8 Hz, 8.1 Hz, Ar-H-7), 7.75 (s, 1H, olefinic proton), 7.54 (dd, 1H, *J*=1.9 Hz, 7.6 Hz, Ar-H-4), 7.60 (d, 2H, *J* = 7.8 Hz, Ar-H-5$^/$, H-6$^/$), 8.20 (d, 2H, *J* = 9.0 Hz, Ar-H-2$^/$, H-3$^/$). ^{13}C NMR ($CDCl_3$) δ 40.40, 40.47, 111.42, 121.42, 123.48, 125.08, 125.74, 127.61, 128.90, 131.97, 132.90, 135.55, 136.04, 141.02, 141.07, 152.28, 195.41. *Anal.* Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98, Found C, 72.60; H, 5.30; N, 5.01.

(*Z*)-3-(4-Isopropylbenzylidenyl)-3*H*-benzo[*b*]thiophen-2-one (8e)

This compound was obtained as a yellow liquid, IR (neat) ν 1701 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.31 (d, *J* = 7.6 Hz, 6H, -CH-(C<u>H</u>$_3$)$_2$), 3.00 (m, 1H, -C<u>H</u>-$(CH_3)_2$, 7.05 (ddd, 1H, *J*=1.2 Hz, 6.7 Hz, 7.5 Hz, Ar-H-6), 7.29 (m, 2H, Ar-H-5, H-7), 7.39 (d, 2H, *J* = 7.8 Hz, Ar-H-5′, H-6′), 7.71 (d, 2H, *J* = 7.8 Hz, Ar-H-2′, H-3′), 7.80 (s, 1H, olefinic proton), 7.92 (dd, 1H, *J* = 1.2 Hz, 7.8 Hz, Ar-H-4). ^{13}C NMR ($CDCl_3$) δ 23.91, 24.12, 34.81, 123.83, 124.45, 125.89, 126.72, 127.30, 127.48, 129.76, 130.16, 130.32, 132.79, 135.01, 156.42, 192.08. *Anal.* Calcd for $C_{18}H_{16}OS$: C, 77.11; H, 5.75. Found: C, 77.13; H, 5.75.

Preparation of 2-oxo-2,3-dihydrobenzo[*b*]thiophene (10)

To a well stirred solution of THF (10 mL) and BuLi [1.6 mL of 1.5 (M) solution in hexane] kept at –78 ℃ under argon atmosphere, diisopropylamine (0.45 g, 0.6 mL) was added through needle syringe system. The reaction mixture was allowed to warm to –20 ˚C and was kept at that temperature for 45 min. A solution of *N,N*-diethylthiocarbamic acid *S*-*o*-tolyl ester (0.37 g, 1.6 mmol) in THF (3 mL) was slowly added at the same temperature. The reaction mixture was stirred for 1 h at –20 ^{0}C and allowed to reach ambient temperature and kept overnight. Then the reaction mixture was cooled to 0 ^{0}C and 5% HCl (10 mL) was added, and the mixture was stirred for 15 min, extracted with CH_2Cl_2 (100 mL), washed with water (3x100 mL), then dried (Na_2SO_4). Evaporation of solvent provided the crude product which was purified by silica gel column chromatography using 20% ethyl acetate-hexane as the eluent to give **10** (0.117 mg, 78%) as colorless crystals, mp 43-44 ^{0}C (lit.,[7] 43.5-44.0 ^{0}C). ^1H NMR ($CDCl_3$) δ 3.56 (s, 2H), 6.92 (m, 1H), 7.02, (m, 1H), 7.22 (m, 2H). ^{13}C NMR δ 36.8, 110.32, 122.70, 124.92, 125.71, 128.32, 143.20, 178.92.

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